

The Development and Clinical Application
of Part Body Neutron Activation Analysis
using Californium-252.

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DECLARATION

The substance of this thesis is the work of the author unless otherwise stated. The clinical studies were undertaken in collaboration with medical colleagues: Dr. J.N. MacPherson and Dr. R. Winney were involved with the renal osteodystrophy study, Dr. I. Chew with the anticonvulsant osteomalacia and lithium carbonate studies and Dr. L. MacIntosh with the spine and thyrotoxic osteodystrophy studies.

M.A. Smith

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ABSTRACT

Californium 252 sources were used in a clinical environment for neutron activation analysis studies for a period of $2\frac{1}{2}$ years. During this period changes in part body calcium in bone, in response to different treatment regimes, were measured in patients suffering from primary or secondary bone disease.

Measurements were performed on peripheral bone, in particular the forearm, using two sources of ^{252}Cf , minimum total activity 56 mCi, and a purpose built partial body counter. Optimisation of the irradiation geometry and the patient irradiation programme enabled calcium measurements to be performed with a precision of between 1.5% and 1.8% and a bone dose less than 3 rem.

The following clinical studies were undertaken: the effect of 1- α -hydroxycholecalciferol on 19 patients undergoing chronic haemodialysis, the use of vitamin D₂ or D₃ in the treatment of 33 patients with potential anticonvulsant osteomalacia, the effect of lithium carbonate in 15 patients with manic depression and the efficacy of conventional treatments in combating thyrotoxic osteodystrophy.

Apparatus was also developed to measure calcium changes in the lumbar spine. Two ^{252}Cf sources of total activity 200 mCi were used for irradiation and a whole body counter for detection of the induced activity. A precision of 2% was obtained for patient measurements, with a bone dose of 1.3 rem.

INTRODUCTION

INTRODUCTION

Neutron activation analysis is one of the few available techniques for non-destructive analysis of elemental composition. Hence its potential, as a clinical tool for in-vivo measurements on human subjects, requires evaluation.

Of all the body elements that can be measured using neutron activation analysis, calcium is almost certainly of most interest. The technique of neutron activation analysis is the only non-traumatic method of directly monitoring the calcium status of a patient with a potentially high degree of precision. The purpose of this study was to evaluate neutron activation analysis using Californium-252 in a hospital environment over a three year period. In particular, various forms of bone disease were studied.

A relatively cheap system was developed initially to measure sequential changes of calcium in the forearm. Although the possibility of absolute calcium measurements was investigated during the course of the project, the clinical studies were designed on the basis of the original decision to study sequential changes. This decision was made because it was felt that if absolute measurements were pursued, little or no time would be left for sequential studies. Not only would a large number of normal subjects have to be irradiated, which could be deemed as unethical, but the normal range might

be found to be so large, as the literature suggests, that the technique would be useless as a diagnostic tool.

The main criterion in the design of the apparatus was to obtain a sufficiently high degree of precision with as low a dose and with as little inconvenience to the patient as possible. Another constraint which had to be overcome was the low activity of the radionuclide sources.

In order to evaluate neutron activation analysis, the technique was compared with other methods of monitoring calcium changes. Indirect methods of measuring calcium from changes in the mineral density were used, using a photon absorption technique and also radiographs. In addition, relevant biochemical tests were performed on all the patients. Thus activation analysis was not evaluated in isolation, but could be compared with all other techniques that are readily available.

Although the main purpose was to evaluate the technique, care was taken to choose patient studies that were clinically relevant. The studies can therefore be divided into two categories, the first using the apparatus as a research tool to evaluate treatment regimes in groups of patients and the second using it as an aid in the management of individual patients in response to various treatments.

In addition to the work on the forearm, a technique was developed to measure calcium changes in the lumbar spine. This is the partial body region where calcium losses can be most debilitating and such losses affect

a large proportion of the elderly population. The technique is described in detail, though no patient study results are given as they will not start to appear for two years.

The experimental work described in this thesis can be divided into three main sections. Firstly, a description is given of the apparatus and the methods used for calcium measurements of the forearm. Secondly, the results of the patient studies are presented and intercomparisons between neutron activation analysis of the forearm and other techniques are made. Thirdly, a description is given of the method devised to measure spine calcium using the experience gained from the forearm studies.

CHAPTER 1.

CHAPTER 1.

REVIEW OF IN-VIVO NEUTRON ACTIVATION ANALYSIS

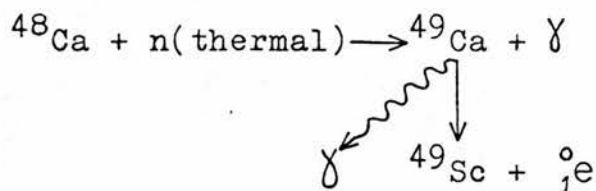
The technique of neutron activation analysis has been in use for in-vivo measurements of body elements in human subjects for the past thirteen years. Absolute levels and sequential changes of about 10 different body elements have been studied in patients with a variety of disorders. In particular, activation analysis is suitable for investigating patients suffering from any form of metabolic bone disease and, in many cases, is the only method of monitoring the efficacy of different treatment regimes. Such clinical investigations using neutron activation analysis have been carried out on a large scale over the past 5 or 6 years.

In this review of in-vivo neutron activation analysis, the emphasis is on techniques that have been used for clinical investigations. Much has been published by research establishments who, possessing a source of neutrons, have carried out "feasibility studies" using phantoms or animals. These have only been included when they are directly relevant to patient studies. In many cases, dose was the limiting factor in human measurements.

1.1 Body Elements Measured by Neutron Activation

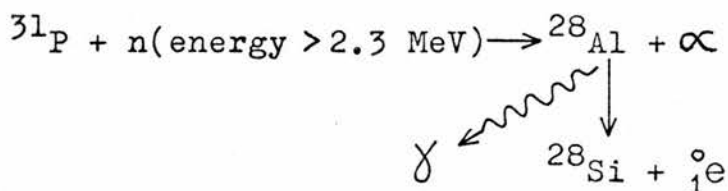
Neutron activation analysis of elemental content has been performed in general using one of three different

types of nuclear reaction. The first, and most common, is where a different unstable isotope of the element is produced after thermal neutron capture. An example of this is ^{48}Ca which, when bombarded with thermal neutrons becomes ^{49}Ca .



Analysis of the induced activity can then be made after the neutron irradiation.

The second type of reaction is when induced activity is again produced but this time only when the incident neutrons are above a certain threshold level. As the neutrons are of a higher energy a (n, α) , (n, p) or $(n, 2n)$ reaction is likely to occur rather than a (n, γ) reaction from thermal neutrons. For example, the following reaction can be used to analyse phosphorus from the measurement of the induced aluminium.



These two different types of reaction are similar in that the measurement of the induced activity and the neutron irradiation occur at separate times.

The third type of reaction concerns the measurement of the prompt gamma after thermal neutron capture. In this case both the irradiation and the detection must be done simultaneously, care being taken to minimise the effect of the gamma spectrum from the neutron source on the detection apparatus. An example of this is the reaction used for the measurement of cadmium.



Table 1.1 contains a list of all the reactions that have been used for measurements on patients. A more extensive list of the first two types of reactions that can be used to measure other elements can be found elsewhere (Glaros 1975).

1.2 Neutron Sources

When reviewing the field of in-vivo neutron activation analysis it must be remembered that more often than not, no choice was available in the source of neutrons used for patient measurements. This was particularly true in the early years where existing apparatus was utilised and the optimum patient irradiation procedure was determined.

The sources that have been used range from large nuclear reactors to small radionuclide sources, with vastly differing neutron spectra, the mean neutron energies ranging from thermal to 14 MeV. The choice of

TABLE 1.1

Reaction	$\sigma(\text{mb})$	Half Life	Principal Energy(s)
<u>(a) Activation by Thermal Neutrons</u>			
$^{48}\text{Ca}(n,\gamma)^{49}\text{Ca}$	1,100	8.8 min	3.10 MeV
$^{23}\text{Na}(n,\gamma)^{24}\text{Na}$	500	15.0 hr	1.37, 2.75 MeV
$^{37}\text{Cl}(n,\gamma)^{38}\text{Cl}$	430	37.3 min	1.64, 2.17 MeV
$^{127}\text{I}(n,\gamma)^{128}\text{I}$	6,200	25.1 min	0.45 MeV
$^{63}\text{Cu}(n,\gamma)^{64}\text{Cu}$	400	12.8 hr	0.51 MeV

(b) Activation by Neutrons above a Threshold Level

	σ at 14 MeV			Threshold
$^{14}\text{N}(n,2n)^{13}\text{N}$	6	10.0 min	0.51 MeV	11.3 MeV
$^{31}\text{P}(n,\alpha)^{28}\text{Al}$	140	2.3 min	1.78 MeV	2.2 MeV
$^{40}\text{Ca}(n,\alpha)^{37}\text{Ar}$	110	35.1 day	2.6 KeV Xray	
$^{56}\text{Fe}(n,p)^{56}\text{Mn}$	100	2.6 hr	0.84 MeV	5.0 MeV

(c) Prompt Gamma Emission after Neutron Capture

$^{14}\text{N}(n,\gamma)^{15}\text{N}$	80	-	10.8 MeV
$^{113}\text{Cd}(n,\gamma)^{114}\text{Cd}$	20,000	-	0.56 MeV

the source depends on the following considerations:-

- (a) The elements to be measured. The spectrum must contain neutrons above any threshold levels required.
- (b) The part of the body to be studied. Soft tissue attenuates neutrons, so higher energy neutrons are required for whole body measurements than part body measurements, to give as uniform a fluence as possible in the region of interest.
- (c) Possible interfering reactions. If neutrons of too high an energy are used, additional unwanted threshold reactions can occur which may cause interference.
- (d) The γ spectrum from the source. If prompt gamma measurements are to be performed, interference from the neutron source must be kept to a minimum.
- (e) The dose to the patient. Too high a neutron energy may unnecessarily increase the dose.
- (f) Finance. Not only the cost of the initial installation must be considered, but also running costs, and replacement costs. The running cost will be higher for a reactor or a cyclotron and replacement cost will be appreciable for neutron generators and the shorter lived radionuclide sources.
- (g) Reliability. The radionuclide sources are

intrinsically the most reliable, but of the other types of source, only the neutron generator has any reputation for unreliability.

Of all the possible neutron sources, radionuclide sources are probably the most suitable for clinical studies in a hospital environment, particularly in the case of partial body calcium measurements. The spectra and properties of the three most common radionuclide sources used for activation analysis are shown in Figure 1.1.

The relatively low mean neutron energy of ^{252}Cf makes it an unsuitable neutron source for threshold reactions listed in Table 1.1b. It does, however, make it ideal for calcium measurements of peripheral body regions because a lower dose per activation can be given compared with other radionuclide sources.

1.3 Whole Body Activation Analysis

The first neutron activation measurements on human subjects were performed by Anderson and colleagues (1964) at Harwell. Two healthy volunteers were measured using a 14 MeV Cockcroft-Walton generator. They were placed 1.1 m from the target and covered with 3 cm premoderator. The subject was irradiated from both sides receiving a dose of 1 rem. After passing urine, the subject was measured for 35 minutes in a whole body counter. Anderson was unable to measure calcium but found that sodium and chlorine were close to ICRP standard man values. The

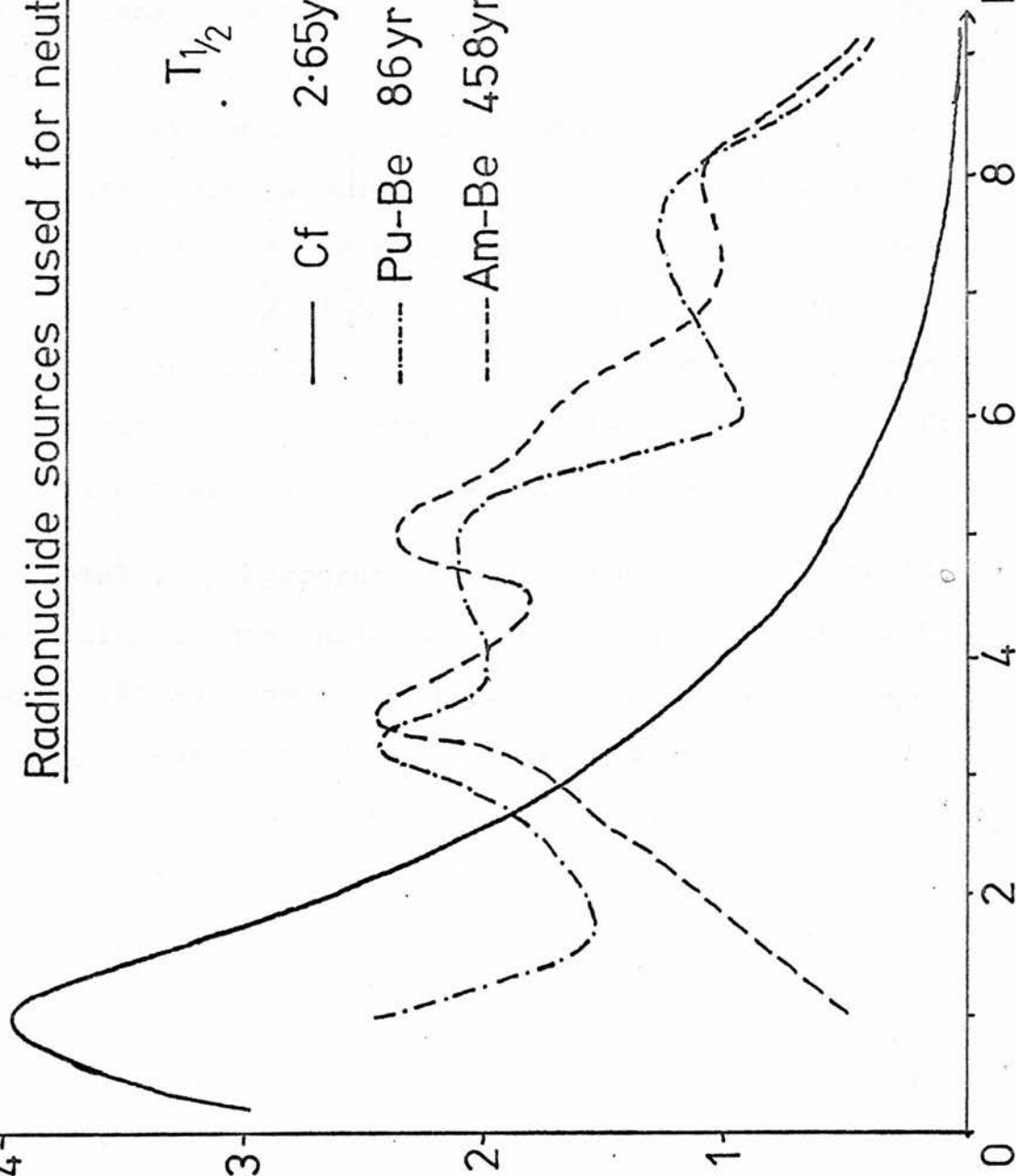
Neutron flux

Figure 1.1

Radionuclide sources used for neutron activation analysis

	$T_{1/2}$	E_n	Volume for 10^8 n.s^{-1}
— Cf	2.65yr	2.35MeV	0.05cm ³
--- Pu-Be	86yr	5.1MeV	19cm ³
---- Am-Be	458yr	5.5MeV	100cm ³

Energy MeV



results also showed little difference between total sodium as determined by neutron activation analysis, and the exchangeable sodium, as measured by isotope dilution.

The errors in the technique were investigated by Battye (1967). He found that in the measurements of Ca, Na and Cl there were interferences of 13.2%, 3.4% and 3.8% from $^{37}\text{Cl}(n,p)^{37}\text{S}$, $^{24}\text{Mg}(n,p)^{24}\text{Na}$ and $^{39}\text{K}(n,2n)^{38\text{m}}\text{K}$ respectively. The effect of using lower energy neutrons for the measurement of sodium was examined. It was found (Newton et al 1969) that serious non-uniformities arose below 2.5 MeV, and 5.2 MeV neutrons from a Van de Graff accelerator were considered optimal. The method of using a 14 MeV generator for sodium measurement was improved (Anderson et al 1972) by scanning the patient, in a tapered wooden coffin, passed a collimated output from the generator. Interfering reactions were corrected for and a value 71.6g/70kg body weight $\pm 4\%$ was obtained.

Total body hydrogen was measured in 27 men and 10 women using cosmic radiation (Rundo and Bunce 1966). The prompt 2.23 MeV gamma radiation was measured and the count rate was found to vary considerably with pressure; 14 c.p.m. at 716 mm Hg and 8.5 c.p.m. at 765 mm Hg. Results showed a hydrogen content of 9.47% body weight for men and 8.65% for women.

Whole body measurements of calcium and sodium were performed in Birmingham using a 60 inch cyclotron. A lithium target bombarded by 10 MeV protons gave a neutron spectrum with an energy range of 1 - 8 MeV, peaking at

3.5 MeV. Initial measurements were performed on 3 cadavers and 3 volunteers (Chamberlain et al 1968a, 1968b). A wooden coffin giving 1.5 cm premoderator was used 2 m from the target. A dose of ~ 1.5 rem was given to the three volunteers, then, after a delay of seven minutes, the induced activity was measured in a whole body counter. Reproducibility of the method from 8 cadaver measurements was 3.7%. Sodium measurements compared with isotope dilution techniques showed there to be a pool of non-exchangeable sodium in the region of 17% (Chamberlain et al 1968c).

For patient measurements, 1.5 cm polypropylene premoderator was used to reduce the variation in the thermal fluence through the first 7 cm to $\pm 15\%$ from the mean (Chamberlain et al 1970). Peaking in the forward direction was reduced by the introduction of an aluminium scattering cone placed in front of the target. Movement of 10 cm by the patient towards the source had negligible effect. The patient was irradiated while lying on his right side facing the source for 3 min. There was a delay of 1 min while the patient was turned over, then a further 2 min 16 s irradiation. The patient was counted in a fixed position for 1024 s in a whole body counter using four 12.1 cm x 10.5 cm NaI detectors. The reproducibility of the method was estimated to be $\pm 5\%$ (Chamberlain and Fremlin 1971). The technique was improved by using an 8 crystal whole body counter and a precision of $\pm 2\%$ for a 1.0 rem dose was obtained (Fremlin et al 1977).

A 14 MeV neutron generator was used in Brookhaven to measure total body calcium (Cohn et al 1970). The subject stood on a turntable 1.5 m from the source with 3.8 cm of premoderator in front and behind. Irradiation was for 163 s then 133 s giving a total dose of 0.637 rem. Following a delay of 5 - 6 min, the induced activity was repeatedly measured for 15 min using a whole body counter consisting of fifty-four 15 cm x 5 cm NaI detectors (Cohn et al 1969). Phantoms containing calcium were measured and the average difference between the real and measured value was 1.73%. Precision and accuracy of the method was therefore estimated to be 1.7%.

The apparatus was used to measure simultaneously Ca, Na, Cl, N and P (Cohn and Dombrowski 1971a). The uniformity of thermal neutron fluence was $\pm 5\%$ and the maximum variation of fast fluence through an average patient was $\sim \pm 20\%$. Three repeated measurements were performed using an Alderson phantom and the reproducibility was 1.98%, 0.74%, 3.20%, 4.40% and 3.38% for Ca, Na, Cl, N and P respectively. Seventeen patients were studied and the lean body mass derived from ^{40}K counts, was found to be a good index with which to normalise the activation results.

Apparatus was built to use the University of Washington 60 inch cyclotron for patient measurements following feasibility studies on phantoms and cadavers. These results suggested that for a dose of 1 rem, total body calcium could be measured with a precision of $\pm 1\%$

and an accuracy of $\pm 8\%$ (Palmer et al 1967, 1968). The neutron spectrum ranged from 4 to 12 MeV with a peak at 8 MeV and was produced by bombarding a beryllium target with 22 MeV deuterons. For patient measurements (Nelp et al 1970) the subject stood in an enclosure 4.5 m from the target where the uniformity of fluence along the body was $\pm 7\%$. The subject stood with his arms and legs inside perspex cylinders which were filled with water and a perspex cylinder was lowered over the head. This improved the uniformity of activation over all the skeleton to $\pm 5.6\%$, and apart from the water and perspex cylinders, no premoderator was used. Bilateral irradiation delivered 2.1 rem to the patient who was then measured for 12 minutes on a whole body counter incorporating four 24 cm x 10 cm NaI detectors, the bed of which moved at an exponentially decreasing speed. Repeated activation of cadavers gave a reproducibility of 0.6 to 1.6% and the combined estimate of the precision was 2%.

With a view to performing absolute calcium measurements, 5 cadavers were measured then ashed (Nelp et al 1972a). The value of calcium per gram bone ash was constant, as was the phosphorus to ash ratio. A relationship was found between calcium in grams and the cube of the cadaver height.

$$\text{Ca in gms} = 0.203 \times \text{ht}^3(\text{m}) \quad \text{for normal men}$$

The accuracy of the measurement was stated to be $\pm 5.2\%$.

A method for measuring whole body nitrogen was

developed in Birmingham utilizing the prompt gamma radiation emitted by ^{15}N after thermal neutron capture. Initial animal experiments on the cyclotron (Biggin and Morgan 1971) showed that sequential measurements of N, C and O would be possible in patients. However for nitrogen measurements it was suggested that 14 MeV neutrons would be more suitable as neither carbon nor oxygen would then be activated. A cyclotron had a great advantage when measuring nitrogen because the neutron beam could be pulsed and so reduce the background in the counting apparatus. The technique used varied slightly from one publication to another (Biggin et al 1972a, Chamberlain and Fremlin 1972, Biggin et al 1972b) but essentially the neutrons were collimated vertically and passed through a patient on a bed which moved through the beam. Two 15 cm x 15 cm NaI detectors were positioned either side of the patient and one 12.7 cm x 12.7 cm NaI detector above, but not in direct line with, the neutron beam. The fast neutrons took about 15 μs to slow down so both the irradiation and counting was pulsed as follows; 15 μs irradiation, 5 μs wait, 150 μs count. For a total body dose of 0.1 rem, the measurement time was about 30 min for the whole body or 18 min when the head, shins and feet were excluded. Phantom measurements suggested the statistical accuracy to be 1%.

After using a neutron generator for several years for neutron activation analysis, Cohn and his colleagues at Brookhaven developed the first purpose-built apparatus

for patient irradiation. Radionuclide sources of Pu-Be were used, which they stated as being the ideal source for whole body measurements of Ca, P, Na and Cl (Cohn et al 1973a). Fourteen 50 Ci sources were used, positioned evenly above and below the patient (Cohn et al 1973b). The patient lay horizontally inside a close fitting 1.9 cm thick polyethylene premoderator which could then be wheeled into the irradiation chamber. The neutron fluence variation was $\pm 4\%$ along the mid-axis and $\pm 10\%$ and $\pm 8\%$ along the front and back surface respectively. The variation front to back through the subject, assuming a 1 cm build up layer of tissue, was $\pm 8\%$. A dose of 0.2 rem was given in 5 min to the patient then, after a 3 min delay, a 15 min count was performed on their fifty-four NaI crystal whole body counter.

Reproducibility measurements on an Alderson phantom gave coefficients of variation of 0.99% for Ca (based on 5 measurements) and 3.9%, 2.1% and 1.83% for P, Cl and Na respectively (based on three measurements) (Cohn et al 1972a). This system, as a method for measuring total body calcium was compared with those at Birmingham, Washington and with the neutron generator system at Brookhaven (Cohn et al 1973c). It can be seen that Cohn's Pu-Be system was obviously the superior technique, both with regard to reproducibility and to dose, but this was probably due more to the whole body counter rather than to the irradiation apparatus.

A purpose built neutron irradiation facility

incorporating two sealed tube neutron generators was built in East Kilbride (Boddy et al 1972, 1973a). The tubes were mounted vertically above and below the patient who lay between the tubes on a moving couch. The generators were housed in a concrete shield which acted as a reflector, no premoderator being used. The patient was counted, after 1 min delay, in a whole body counter between two 29 cm x 10 cm NaI detectors on a bed which moved at the same speed as the bed in the irradiation apparatus. Such a short delay time was advantageous for phosphorus determination. The apparatus was designed for simultaneous measurements of Ca, P, Na, Cl and N, the $^{14}\text{N}(n,2n)^{13}\text{N}$ reaction being used for the latter. The root mean square variation of neutron fluence through a man-like phantom was $\pm 2.1\%$ and $\pm 4.5\%$ for fast and thermal neutrons respectively (Boddy et al 1974a). The reproducibility of Ca, P and N measurements using an Alderson phantom was 1.9%, 3.15% and 2.63% respectively for a dose of about 1 rem. (Boddy et al 1973b, 1973c).

A method for measuring total body calcium with a greatly reduced dose was investigated in animals (Palmer 1972, 1973). He used the $^{40}\text{Ca}(n,\alpha)^{37}\text{Ar}$ reaction and found that the time for 95% of the ^{37}Ar to leave the body was 1 hr for rats, $1\frac{1}{2}$ hr for dogs and more than 2 hr for humans. The 2.6 KeV X-rays and Auger electrons from the ^{37}Ar were measured in a proportional counter after being separated from other exhaled gases. The expected dose to humans was estimated to be 0.01 rem.

The method was eventually developed for patient measurements (Lewellen et al 1975) using the Washington cyclotron for patient irradiation. The patient breathed 25% O_2 and 75% He and was then placed on a closed circuit breathing system for 20 - 40 min. After separation from other gases the ^{37}Ar was finally counted between two 23 cm x 10 cm NaI detectors for between 4 to 12 hours. Whole body calcium was measured simultaneously on patients using both the ^{37}Ar and conventional ^{49}Ca methods. Excretion rate at 30 min correlated well with total body calcium in 10 patients ($r = 0.97$). In 16 patients studied, the maximum excretion occurred at 5 - 20 min after irradiation and the curve could be described by a double exponential. The average half times of the two components were found to be 27 min and 156 min. This compared with values of 16 min and 30 hr from a single subject from similar work done at Birmingham (Ozbas et al 1976). Both groups estimated that dose levels to patients would be ~ 0.1 rem and Washington suggest that a precision of 1% in a 3 hr sample would be possible using 14 MeV neutrons.

Whole body calcium measurements were performed using the M.R.C. cyclotron at Hammersmith (Spinks et al 1976b). The patient stood upright sandwiched between two 5.5 cm sheets of premoderator, a distance of 4 m from the target emitting neutrons with a mean energy of 7.5 MeV. The variation in neutron fluence was $\pm 5\%$ and $\pm 12\%$ along and within the patient. After bilateral irradiation and a

dose of 1 rem there followed a delay of 3 min and then the patient was counted in a steel room by ten 15 cm x 10 cm NaI detectors. Six repeated measurements using a cadaver gave a C.V. of 2%.

Phantom measurements were performed to determine the accuracy of the calcium measurement for absolute determinations of calcium (Spinks et al 1977). Using two different size phantoms and measuring the effect of overlying soft tissue the accuracy of the measurement was estimated to be $\pm 8\%$.

Using the methods described in this section it can be seen that whole body calcium could in general be measured with a precision of about 2% though in one case (Cohn et al 1972a) the value was 1%. This value of 1% obtained by Cohn illustrates that not only is a large and expensive neutron source necessary for whole body measurements, but that a similar degree of sophistication is required for the counting apparatus.

The values of the precision that have been quoted may be slightly optimistic because most repeated measurements were performed with phantoms, not with live subjects. In addition some values were based on as few as three repeated measurements and in general not more than six. After expending such effort in designing and constructing the various irradiation apparatuses it is unfortunate that the precision of the techniques was not evaluated more fully.

1.4 Partial Body Activation Analysis

Neutron activation analysis of specific sites in the body has been performed either to investigate individual organs or to measure a value that may reflect the whole body elemental status of a patient. There are several advantages of partial body measurements over whole body measurements. From the financial aspect it is considerably cheaper to construct apparatus for partial body measurements. Secondly, it is better to limit the patient dose to the organ of interest and to avoid unnecessary irradiation of other organs, particularly those which are more radiosensitive. It can also be more desirable to measure changes of an element at a particular site, even if the element is present throughout the body; for example, where changes in calcium in the body are greatest at sites containing trabecular bone. Finally, a patient may find partial body measurements psychologically less traumatic than some of the whole body measuring apparatus, such as those at Brookhaven and Washington. The major disadvantage of measuring the partial body content of an element is when that element occurs throughout the body, and hence absolute values may be difficult to obtain.

The first partial body site to be investigated by neutron activation analysis was the thyroid, investigations being started by two separate groups at around the same time. The workers at East Kilbride (Boddy et al 1973d) measured the total iodine content by monitoring the induced ^{128}I after irradiation by neutrons from their

UTR-100 KW reactor with a maximum yield at about 1 MeV. As ^{128}I has a fairly low energy there was a large background contribution to the spectrum and so the design of the detection equipment was very important to achieve good counting statistics. The counting apparatus used at East Kilbride varied considerably so the accuracy of the technique also varied.

In initial phantom and in-vitro measurements (Boddy 1966), irradiation was for 5 min and detection for 10 min using a single 7.6 cm x 7.6 cm NaI crystal in a whole body counter. For a dose of about 18 rem the minimum detectable amount based on counting statistics was estimated to be 0.65 mg. For clinical studies the patient lay prone on the top of the reactor, his thyroid positioned over the opening of a 15 cm x 7.5 cm collimator for a 5 min period. Counting was then performed using a shadow shield thyroid monitor incorporating a 7.5 cm x 7.5 cm or 12.5 cm x 12.5 cm NaI crystal. Good agreement was found in two patients whose thyroids were measured in-vivo before and in-vitro after thyroidectomy using neutron activation analysis (Boddy and Alexander 1967). The error due to counting statistics and spectral stripping was about 5 to 10%, and the error due to variation in thyroid size, about 6%. In seven patients there was a poor relationship between activation analysis and biochemical measurements of the excised glands (Boddy et al 1968).

With an improved detection system incorporating two crystals, a maximum variation of 14% due to size and position was obtained, the standard deviation being

comparable to that for iodine levels above 4 mg (Boddy et al 1970). The use of a boron absorber to filter the beam was found to give better uniformity through the organ with the effect, however, of reducing the sensitivity (Boddy et al 1971). The final system adopted by East Kilbride for thyroid measurements used a beam size of 15 cm x 10 cm, a dose of 22.5 rem (Boddy et al 1969), a boron absorber and a single 29.2 cm x 10.2 cm NaI detector. The total system error was about 15% (Boddy et al 1973d).

The group in Orsay also used a reactor to investigate the measurement of thyroïdal iodine but the technique differed considerably from that used at East Kilbride. Completely thermalised neutrons were used so the fluence was inhomogenous. To correct for this, ^{129}I was used as an internal standard. The half life of ^{129}I is very long (1.6×10^7 yr) and when it is bombarded by neutrons it yields ^{130}I ($T_{1/2} = 12.5$ hr) and $^{130\text{m}}\text{I}$ ($T_{1/2} = 9.2$ min) with peaks at 540 KeV, 660 KeV and 740 KeV. On the macroscopic scale, the distribution of ^{127}I and ^{129}I were the same and the ^{129}I did not appreciably alter the iodine content of the gland.

Initial experiments were performed on two sheep (Lenihan et al 1968) and good agreement was found between the estimated iodine content and the actual values after the thyroids had been removed. In practice, difficulty was found in resolving the 540 KeV peak of $^{130\text{m}}\text{I}$ and the 510 KeV peak associated with the annihilation radiation from other elements (Lenihan et al 1967). Measurements

were performed using this technique on a group of 11 patients, of which five were euthyroid and six had endemic goitres (Rivière et al 1970).

The reactor at Orsay was also used for bone mineral measurements of the tibia in three volunteers, one of whom had a callous from an old fracture (Comar et al 1968). Thermal neutrons from the reactor, after passing through a 2 cm x 5 cm collimator, were directed against the antero-medial surface of the tibia. A 20 cm³ Ge(Li) detector, 10 cm from the leg, was used to measure the spectrum from thermal neutron capture during the 10 to 30 min irradiation. Three peaks were seen, 5.090 MeV and 5.598 MeV from chlorine and 5.393 MeV from calcium, although the sensitivity was very low. At the end of the irradiation, the induced activity from ⁴⁹Ca, ²⁴Na and ³⁷Cl was measured using a 20 cm x 10 cm NaI detector surrounded by 4 cm thick lead with a 6 cm diameter opening. The ratios Ca/Na, Ca/Cl and Na/Cl were investigated for up to half an hour after irradiation. For a dose of 7 rem it was stated that the reproducibility was adequate for sequential studies.

This same reactor was used to measure the Ca/P mass ratio using Na as an internal standard (Comar et al 1970). The prompt γ rays of phosphorus (77.2 KeV) and sodium (90 KeV) were measured using a 1 cm² planar Ge(Li) drift detector. At the end of the irradiation the ⁴⁹Ca/²⁴Na ratio was calculated, hence sodium could be used as an internal standard. The Ca/P values obtained in two

patients were 2.9 and 2.6. These were higher than the accepted values, probably due to the effect of recirculation in the soft tissue. Acceptable reproducibility figures could only be achieved by using a much larger planar Ge(Li) detector.

Partial body calcium measurements were performed in Toronto using Pu-Be sources (McNeill and Agard 1969, Agard et al 1971). Four sources, each of 5 Ci were immersed in an aqueous medium and arranged to give a relatively uniform flux in the region of the os calcis. After a 10 min irradiation and 3 min delay, the induced ^{49}Ca was measured for 10 min between two 20 cm x 10 cm NaI detectors located in a whole body counter. Using a Rando phantom, a net count of 1800 was obtained for a dose of 1 rem. The reproducibility of the method was about 4% (McNeill et al 1970). No patient measurements were reported with this system and the sources were incorporated in apparatus to measure calcium in the trunk.

It was thought that partial body calcium measurements of the trunk would have advantages over whole body measurements because larger percentage changes would occur (McNeill et al 1973b). Twelve 5 Ci Pu-Be sources were placed symmetrically above and below the trunk with a source to skin distance of approximately 12 cm. Hydrogenous reflectors, 30 cm thick, were fixed above and below the sources and 4 cm thick wooden premoderators were used. The thermal neutron fluence, to the 50% level, covered an area 60 cm x 30 cm, so for a 6 ft subject,

30% of the total bone was viewed whereas for a 4 ft subject, the figure was 60%. The variation in thermal fluence was $\pm 5\%$ anterior to posterior, and $\pm 20\%$ along the length of the measured region (McNeill et al 1971). Irradiation and delay times were 20 min and 3 min, after which the subject was counted for 20 min using four 20 cm x 10 cm NaI detectors positioned along the mid-line. A dose of 0.4 rem was received by the patient and approximately 1000 net counts were obtained from ^{49}Ca . The effect of body thickness was investigated and results using an Aldersen phantom gave an error of 5%/cm body thickness (McNeill et al 1974). The overall reproducibility of the method, based on measurements of normal volunteers, was quoted as 6.4%. Extensive patient measurements, both sequential and absolute, were performed using a calcium index based on 16 normals, and a correction for body thickness.

$$\text{Calcium index: Counts} = 207(\text{height})^3 + 17$$

$$\text{Thickness} = 1.46\sqrt{W/H} - 6.23$$

(Harrison et al 1975)

Calcium measurements of the hand, which contains large amounts of trabecular bone, were performed in Aberdeen using a single 25 Ci Am-Be source (Catto et al 1973a). The source was placed inside a perspex tube with a wall thickness of 1 cm which was in the centre of a water tank. The perspex tube was gripped by the patient for 1000 s after which the hand was counted between two 13 cm x 10 cm NaI detectors for 2000 s. The dose was originally quoted as 5 rem per measurement, but this has

since been checked and found to be 15 rem (Ettinger 1975). Reproducibility measurements using nine cadaver hands gave a value of C.V. = 5% and the calcium values obtained by neutron activation analysis compared well with the ashed values of five of the hands. The apparatus was used to monitor changes in patients undergoing chronic haemodialysis.

A system was designed to measure the levels of cadmium in the liver using the cyclotron at Birmingham (McLellan et al 1975). The patient lay in a semi-prone position and the liver was irradiated from below by a vertical beam of neutrons which was pulsed to reduce the background gamma radiation. The 0.559 MeV prompt gammas were detected by a Ge(Li) detector. Phantom measurements suggested that small variations in the patient's position gave an accuracy to within $\pm 5\%$ and a dose of 0.4 rad was required to detect low Cd levels in the region of 0.5 p.p.m. A portable system was also developed using a single Pu-Be source (Thomas et al 1976) which had a relatively low gamma background. It was also found that for considerably enlarged livers the maximum error in a measurement was 20%. Both methods were used to detect toxic levels of Cd in factory workers.

The Hammersmith cyclotron was used to measure the retention function of sodium in the hand (Spinks et al 1976a). The patient's hand was placed in a premoderator glove and given a dose of 1.5 rad during a 30 sec irradiation. The patient's hand was then measured between

two 15 cm x 10 cm NaI detectors for 20 min at intervals from 3 min to 48 hr after irradiation. It was found that the retention function of the ^{24}Na could be expressed as two exponentials, or better still as a power function. This retention function was then studied in patients with a range of metabolic bone diseases.

Calcium measurements of the hand have been performed in Lyons using ^{252}Cf (Guey et al 1976). The irradiation geometry resembled that of Catto described previously. A single 75 mCi source was used inside a perspex tube of wall thickness 1.25 cm which the patient gripped, and this was surrounded by 200 litres of water. After an irradiation of 600 s and a delay of 30 s the hand was counted for 600 s between two 15 cm x 10 cm NaI detectors. The dose to the hand was 2 rem and approximately 4500 gross counts were obtained in the ^{49}Ca region. The apparatus has been used primarily for measurements on patients with chronic renal insufficiency.

A method for measuring both calcium and phosphorus in the hand was developed using sources of ^{252}Cf and Pu-Be together (Maziere and Comar 1976). Two 100 mCi sources of ^{252}Cf and four 10 Ci sources of Pu-Be were arranged in a circle of diameter 12 cm. The subject's hand entered a tube and gripped a hand grip, which was surrounded by the ring of sources, at the centre of a 1 m cube wax block. A dose of 8 rem was given during a 5 min irradiation and after a 45 s delay the hand gripped a rod between two 12.5 cm x 12.5 cm NaI detectors for an

8 min and 24 min count. On phantom measurements the statistical error was 2.5% for P and 1.6% for Ca and the reproducibility from measurements on a skeletal hand was within 3% for both.

The first partial body measurements of the spine were performed using the Birmingham cyclotron to measure calcium and phosphorus (Al-Hiti et al 1976a). The patient was irradiated sitting upright in a chair which was elevated so that the lumbar region of the spine was level with, and facing the target. Fast neutrons with mean energy 3.5 MeV were collimated to a 20 cm x 10 cm region of the spine and a dose of 3 rem to the spine was given in 150 s. After a delay of 150 s the induced activity was measured for four 5 min periods with the subject sitting upright on a seat with his spine against a single 15 cm x 15 cm NaI detector. Unilateral irradiation and detection could produce large positional errors and to minimise this a small ^{137}Cs source was attached to the patient to correct for any error in positioning during counting. Repeated measurements on several volunteers gave a reproducibility of $\pm 3\%$ (Al-Hiti et al 1976b).

A comparison of all the techniques used for measuring partial body calcium in patients is given in Table 1.2.

1.5 Clinical Results using In-Vivo Neutron Activation Analysis

Neutron activation analysis has been performed on large groups of patients in different centres to assess

TABLE 1.2

Techniques for Partial Body Calcium Measurements

Centre	Site	Source	Total Acti- vity	T _I	T _D	T _C	Detectors	Approx. net ⁴⁹ Ca Counts	Dose	Pre- cision
Toronto (McNeill et al)	Trunk	12 Pu-Be	60 Ci	20min	3min	20min	4 20cm x 10cm NaI	1000	0.4 rem	6.4%
Aberdeen (Catto et al)	Hand	1 Am-Be	25 Ci	1000s		2000s	2 13cm x 10cm NaI	1300	15 rem	5%
Lyons (Guey et al)	Hand	1 ²⁵² Cf	75mCi	600s	30s	600s	2 15cm x 10cm NaI	4500	2 rem	
Orsay (Maziere et al)	Hand	2 ²⁵² Cf 4 Pu-Be	100mCi 40 Ci	5min	45s	8min 24min	2 13cm x 13cm NaI	3800	8 rem	3%
Birmingham (Al-Hiti et al)	Spine	Cyclotron	-	150s	150s	4 x 5 min	1 15cm x 15cm NaI	1400	3 rem	3%

either the normal level of a particular body element, the level of an element when a patient is suffering from a particular disease or to assess the efficacy of different forms of treatment. Many patients, however, have also been irradiated simply to validate the technique of neutron activation analysis, or a particular piece of apparatus. Such patient measurements, or data obtained on individual patients, will not be discussed here; rather the emphasis will be placed on studies conducted to obtain clinical information relevant to the treatment of future patients. Such studies will serve as a more valuable evaluation of neutron activation analysis.

(a) Non-Exchangeable Sodium:

Whole body sodium has been measured both by neutron activation analysis and by isotope dilution techniques, the latter measuring the exchangeable sodium present. In the first whole body neutron activation measurements (Anderson et al 1964) no evidence was found for a non-exchangeable sodium pool. However, evidence was later produced for a non-exchangeable pool of about 17% by the Birmingham group (Chamberlain et al 1968c). An even higher value of 27% based on results from five patients was found in Washington (Rudd et al 1972).

(b) Renal Disease:

Long term total body calcium measurements were performed on a group of 27 patients on maintenance renal dialysis (Denney et al 1972, 1973). Correlation with bone histology showed that patients with "osteomalacia"

had the lower total body calcium (88% of normal) and those with fibrosis, the highest (108% of normal). Patients with fibrotic and histologic bone patterns showed relatively stable calcium balance while all the other types were negative. The dialysate bath calcium was increased from 3 to 4 mEq.ml⁻¹ and a shift was detected towards positive calcium balance.

Absolute values of body composition were measured in 6 uremic and 11 dialysis patients using the 14 MeV generator in Brookhaven (Cohn et al 1972b). Total body calcium was the same as in normals in both groups. The only significant values found were raised sodium levels in uremic patients and losses in dialysis patients when the latter group was followed sequentially.

Sequential partial body calcium measurements of the hand showed a loss over 6 months on 13 dialysis patients with dialysate calcium 5.3 to 5.5 mg per 100 ml (Catto et al 1973b). The mean calcium loss was 10.8% and this was evident in 93% of the patients, though it must be stated that their criterion for a significant change was one greater than 1 S.D. Radiological change was noted in only 15% of the patients.

Total body calcium was measured in 14 unselected cases of chronic renal insufficiency, none of whom required dialysis (Hosking et al 1973). Total body calcium fell in patients with osteomalacia but this change could be reversed with pharmacological doses of vit. D. In those with osteitis fibrosa, total body calcium increased.

In 13 patients with modest to severe renal insufficiency, an effort was made to correlate total body values measured by neutron activation analysis with clinical measurements (Letteri et al 1974). Total body calcium, expressed in absolute terms or as a function of lean body mass, did not correlate with creatinine clearance (glomerular filtration rate), plasma HCO_3 or plasma Ca. However the total body P/Ca ratio was increased in eight out of ten patients with $\text{G.F.R.} < 20 \text{ ml.min}^{-1}$ and all patients with plasma P $> 6 \text{ mg/100 ml}$ had an increased P/Ca ratio.

Partial body calcium measurements were carried out in Toronto on 36 patients less than 55 years old with renal failure and the patient's "bone index" (B.I.) was determined (Harrison et al 1974a). Seventeen had a B.I. below normal, seven of these having no evidence of renal osteodystrophy. Eighteen had a normal B.I. but ten of these had moderate or severe renal osteodystrophy. One had a high B.I. with no evidence of bone disease. Following treatment with vitamin D some patients with renal osteodystrophy increased their B.I. by 20% - 25%, to normal or above normal values.

The effect of 1- α -hydroxycholecalciferol, a vitamin D analogue, on renal osteodystrophy was monitored both by whole body and part body activation analysis and will be discussed in detail in Chapter 7.

(c) Osteoporosis:

The effect of treatment of osteoporosis has always been difficult to assess because any changes are so small. The fact that small changes can be detected over a fairly short period makes neutron activation analysis the ideal method of monitoring the treatments of osteoporosis.

Whole body calcium was measured in seven patients over a period of 3 months during which time they were treated with porcine calcitonin together with dietary Ca and P supplements (Cohn et al 1971b). After this time, three of the patients had increased their Ca by amounts greater than 1.9%, the precision of the technique. The lack of a control group and the fact that only three patients responded makes the study inconclusive.

The same technique was used on eight patients before, and 2 to 7 months after, treatment with fluoride (Cohn et al 1971c). No significant increase was recorded in any of the patients, though over such a short time period and in such a small group this is perhaps not a conclusive result.

The group in Washington performed whole body measurements for longer periods. Five women with idiopathic osteoporosis were given a series of intravenous calcium infusions for between 12 and 15 months (Dudl et al 1973). No patient showed improvement and the loss of total body calcium was similar to untreated osteoporosis.

The same apparatus was used on 26 postmenopausal osteoporotic females to test the effect of dianabol

(Chestnut et al 1974, 1975). The patients were divided into two groups of thirteen; one group receiving 5 mg dianabol and the other a placebo. Six patients on placebo and ten on dianabol completed the two year study showing a significant decrease (3.1%, $p < 0.005$) in total body calcium in the former and an increase (2.0%, $p < 0.10$) in the latter. The difference between the two groups was found to be very significant ($p < 0.01$).

Seven patients with Cushing's syndrome were monitored before treatment and all except one was treated surgically (Aloia et al 1974). Four of the patients were followed for up to 25 months and two of these exhibited a significant increase in total body calcium following therapy. These patients were however aged 14 and 21, so the increase could be due to growth rather than the reversing of the osteoporosis following the correction of hypercortisolism. The mean total body P increased to a great extent post-operatively.

(d) Parathyroid Dysfunction:

Ten cases of primary hyperparathyroidism were studied for up to two years in Birmingham (Hosking et al 1972a). Seven of the cases had successful surgery but the response to parathyroidectomy was variable. No correlation was found between post-operative changes in calcium content, parathyroid size and histology, nor with the mode of clinical presentation. It was suggested that absolute measurements would be of more use, as any decreases may be due to a return to the normal calcium level.

Absolute levels of Ca and P were measured in nine hyperparathyroid patients, eight of whom were untreated and in three hypoparathyroid patients using whole body activation analysis (Cohn et al 1973e). In the patients with hyperparathyroidism, three were within the normal Ca range and six had a mean calcium 85% of normal. A low mean value of P/Ca was found - consistent with PO_4 loss. In the three patients with hypoparathyroidism, the bone calcium levels were raised as would be expected.

(e) Osteomalacia:

In Toronto, part body calcium measurements were performed on four patients with active osteomalacia and an increase of 30% after 2 to 6 months on treatment was reported (Harrison et al 1972, McNeill and Harrison 1973a). Calcium measurements, normalised using the subject's height or arm span, were performed on seven fully grown patients with familiar hypophosphatemic vitamin D refractory rickets (Harrison et al 1976). In the five patients with rachitic deformities the calcium bone index was above normal ($p < 0.002$). In contrast, the two without were in the normal range.

Changes in total body calcium and sodium were measured on six patients receiving different treatments for osteomalacia (Hosking et al 1972b). Each patient showed an increase of between 3% and 30% though only four patients were studied for the complete 24 months. In these patients the increases occurred for the whole period, though complete healing had occurred after 6 months on the

basis of histological examination. In general, as the calcium rose, there was a fall in the non-exchangeable sodium pool in the bone.

Whole body calcium measurements were performed on thirty chronic alcoholics, eighteen with cirrhosis and twelve without, to investigate the reported decrease in bone mass caused by possible vitamin D deficiency due to cirrhosis of the liver. Both total body calcium and bone mineral content did not show any loss in either group of patients (Roginsky et al 1976).

(f) Paget's Disease:

Twenty patients were treated with calcitonin and whole body calcium measurements were performed (Wallach et al 1975). Despite clinical improvements, seven out of the fifteen who completed the study showed partial or total loss of the initial decelerating effect of calcitonin on skeletal turnover, whereas the remaining eight maintained it. Changes in the skeletal turnover were roughly proportional to changes in alkaline phosphatase and urine hydroxyproline. The mean total body calcium was raised by 22% compared with normals prior to treatment and after treatment the mean was decreased by 4%, the change being significant.

(g) Acromegaly:

Whole body Ca, Na, Cl, P, N and K were measured in ten patients (Aloia et al 1972). Total body calcium was raised in all but two and in some cases strikingly so. The ratio Ca/K was decreased in all cases and the observed

changes in K, N, Na and P were similar to those produced by chronic administration of growth hormone to normal subjects.

(h) Cadmium Toxicity:

The partial body measurement of cadmium in the liver has proved very effective in detecting quantities absorbed by industrial workers. The level in patients was found to be between 0 - 2 p.p.m. whereas the levels in works "at risk" were between 35 p.p.m. and 200 p.p.m. (Harvey et al 1975).

1.6 Comparison of Neutron Activation Analysis and Densitometry

The method of measuring bone mineral content using a photon absorption technique (Cameron et al 1963) is widely used. As its main function is to monitor calcium loss, it is important to compare it with neutron activation analysis.

Whole body activation analysis was compared with densitometry at six sites of the radius, ulna and humerus (Chestnut et al 1973a, 1973b) in fourteen osteoporotic patients. There was good correlation at all six sites, the correlation coefficient ranging from $r = 0.94$ to $r = 0.84$. When, however, both the methods of measurement were normalised, the correlation was much worse; $r = 0.79$ at the site where previously $r = 0.94$ (Manzke et al 1975).

In Brookhaven, whole body calcium was compared with densitometry of the radius 8 cm from the distal end, in

six different patient groups including normals. The correlation coefficients ranged from $r = 0.826$ for the osteoporotic group to $r = 0.973$ for normals (Cohn et al 1973d). The values from the forty osteoporotic patients were normalised, total body calcium with ^{40}K and the bone mineral content with the width of the radius. Correlation then became $r = 0.454$ (Cohn et al 1974). Thirty-four of these patients, most having vertebral compression fractures, were studied over an interval of about 9 months. Most patients displayed a change in total body calcium and bone mineral content that was at least twice the precision of the method. No correlation was found between the changes measured by both methods ($r = 0.17$) (Aloia et al 1975). A similar trial was carried out with twenty-five patients with severe chronic renal failure and fifty-three patients with severe uremia who were on dialysis (Cohn et al 1975, 1976). Correlation coefficients of $r = 0.919$ and $r = 0.892$ were obtained on the two groups respectively, when absolute measurements were compared. However the correlation between changes over a time period in all seventy-eight patients was poor ($r = 0.25$).

Comparisons between partial body calcium content and densitometry have not been made so thoroughly. The calcium content of the trunk was compared with densitometry of the radius in seventy-one individuals and a correlation coefficient $r = 0.76$ was obtained. Twenty-seven patients were also measured sequentially to compare the changes measured by both methods. "Reasonable

agreement" was obtained in twenty-one out of twenty-seven and a marked discrepancy in three cases (Harrison et al 1974b).

Densitometry of the same site was compared with activation analysis of the hand in thirteen dialysis patients (Catto et al 1973b). The mean calcium loss was 10.8%, evident in twelve patients whereas the mean mineral loss was 3.8%, evident in seven patients. Unfortunately no correlation figures were given.

A good correlation was obtained between activation analysis and densitometry results in all the studies simply because the stature of the patient was reflected in both measurements. Thus when the effect of size was reduced by normalisation, the correlation was worse. The most important results were the correlations between the changes measured by both methods. The poor correlations that were obtained still leave two major questions unanswered. Firstly, does neutron activation analysis of calcium measure the same thing as densitometry and secondly, even if it did, would changes in the radius reflect changes in the overall calcium status of a patient? Before answering the second question an effort must be made to answer the first. An attempt is made in this thesis by performing neutron activation analysis and photon densitometry at the same site.

CHAPTER 2.

CHAPTER 2

IRRADIATION APPARATUS

2.1 Neutron Sources

Two sources of Californium -252 were used for the neutron activation analysis measurements. Californium -252 produces a typical fission neutron spectrum (Fig.1.1) which can be represented by the Watt formula:-

$$N(E) = 0.373e^{-0.88E} \sinh (2.0E)^{\frac{1}{2}}$$

where $N(E)$ = fraction of neutrons/unit energy range
and E = energy in MeV

The mean energy of ^{252}Cf is in the region of 2.35 MeV (Meadows 1967) and it decays with an effective half life (alpha and spontaneous fission) of 2.65 years (Amersham). Its high specific neutron emission, 2.3×10^9 neutrons. $\text{sec}^{-1} \text{ mg}^{-1}$, means that sources used for patient irradiations can be very compact. The relatively low mean energy makes it an ideal radionuclide source for partial body measurements at peripheral sites of elements activated by thermal neutrons.

The two sources of ^{252}Cf arrived at the Western General Hospital in January 1975, each of activity approximately 51 mCi. The sources had previously been used for about 3 years at the Scottish Universities Research and Reactor Centre (S.U.R.R.C) in East Kilbride where some of the initial physical evaluation was performed.

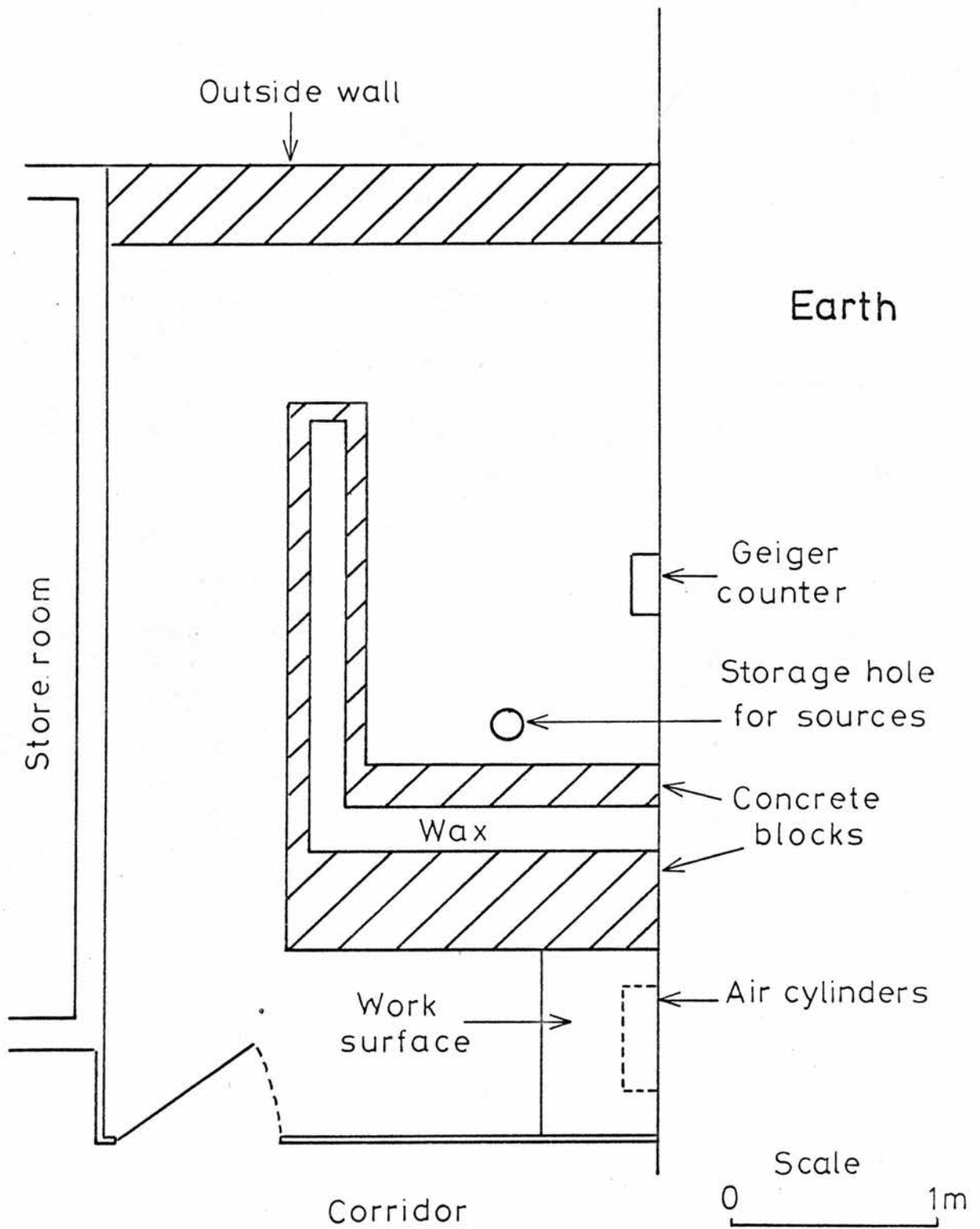
The ideal ^{252}Cf source activity for patient measurements was stated as being 200 mCi (Boddy et al 1974b) while a feasibility study carried out in America stated it to be between 500 mCi and 1500 mCi (Evans et al 1976). However the half life of ^{252}Cf meant that our patient measurements would have to be performed with a total combined source activity eventually as low as about 50 mCi, so the system was designed accordingly. In fact, it was possible to replace the sources in March 1977 with two sources each of activity 104 mCi, which were purchased to extend the existing studies over a longer time period and to enable partial body measurements of the lower spine to commence.

2.2 Irradiation Chamber

The room constructed for patient irradiation was situated in the basement of the hospital, in what was originally the blank end of a corridor, about 20 m from the room containing the counting apparatus. An L-shaped baffle was constructed from concrete blocks and paraffin wax from floor to ceiling (Fig. 2.1), to provide shielding for the operator and other hospital personnel. In addition, one outside wall had to be thickened with an extra layer of concrete blocks to reduce the dose on the outside of the hospital. A layer of wax blocks, between 6 and 8 inches thick, was also placed in the ceiling space above the inner section of the chamber to reduce the dose to the casualty ward directly above. The fire safety officer was

Figure 2.1

Scale diagram of activation chamber



informed of the wax in the ceiling space and he was of the opinion that it did not constitute a fire hazard.

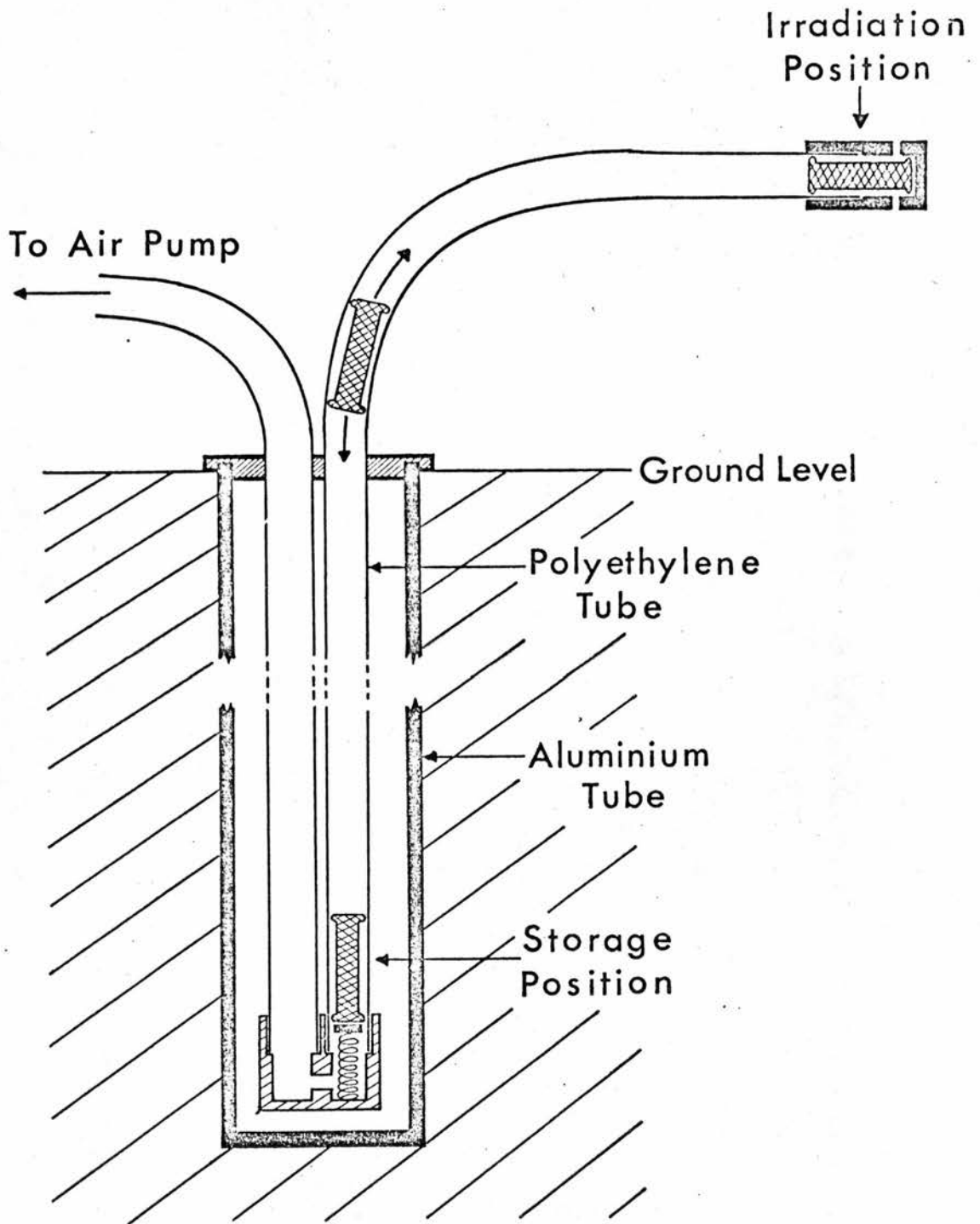
The neutron and gamma dose was measured, using rem counters, with the sources in the "worst" position, that is with no reflector or premoderator round them. The dose levels were less than 1 mrem.hr^{-1} at the operator position and less than 0.3 mrem.hr^{-1} at floor level in the ward above.

The two sources were stored 3 m below ground when not in use and could be delivered pneumatically to the chosen irradiation position above ground (Fig. 2.2). This pneumatic delivery system was developed at S.U.R.R.C. in East Kilbride for the cylinders encapsulating the sources (Glaros 1975). The motor and air cylinder were stored under the work surface behind a false wall and two polythene air tubes passed through the shielding wall and down the storage hole. The source cylinder delivery tubes were made of strong polyethylene with a metal cap at the end with holes in to allow the air to escape. The sources could be delivered swiftly to the irradiation position and back again when required with little or no error in timing. Inductance coils were designed originally as part of the system at East Kilbride to monitor the position of the sources and to control the timing. These proved unworkable, and as the sources gave an audible click when they reached the irradiation position and a rush of air when they left, it was easily possible for the operator to time the irradiation to within 0.5 s with a stop-watch. This degree of error would only start to become significant



Figure 2.2

Pneumatic delivery system



for patient irradiation times of less than 1 min, which is much shorter than that which was actually used.

A geiger counter was fixed inside the activation chamber with a remote control box by the operator position. A green or red light on the box acted as a safety device to check that the sources were in the safe position below ground before the operator entered.

During the two and a half year period since the sources were installed, neither of the two personnel concerned with patient or research experiments received any measurable neutron dose, as detected by both fast and slow neutron film badges.

2.3 Partial Body Irradiation Sites

As far as neutron activation analysis is concerned, the element that is of most clinical interest is calcium in the bone. Careful consideration had to be given to achieve the optimum patient irradiation geometry at the most suitable body site. Although regions such as the spine are of great clinical interest it was decided to commence activation measurements at a peripheral site whilst a method for spine measurements was being developed. Out of the four main peripheral body regions, the forearm was chosen as the most suitable site for the majority of patient studies. This is not to say that the forearm is superior in all respects to the other sites but rather that it offered the best compromise of the following characteristics:-

- (a) The quantity of calcium present. As the isotope of calcium which becomes activated, ^{48}Ca , is only 0.186% abundant, the body site chosen must have sufficient calcium present to achieve adequate counting statistics. The approximate percentage of the skeleton in the peripheral sites is 2.68% in the radius and ulna, 1.52% in the hand and wrist, 6.33% in the tibia and fibula and 5.82% in the foot (Spiers and Burch 1957). However, because of the size of the different regions, the efficiency of activation and detection multiplied by the amount of calcium present, gives a comparable number of calcium counts in all four regions for a given dose.
- (b) Uniformity and size of the bone. The long bones of the forearm and lower leg are the most uniform and so would probably give better precision results with bilateral irradiation. Also the wider the bone, the greater the non-uniformity of thermal neutron flux through the bone and hence the precision would be worse.
- (c) The likelihood of calcium changes occurring. Calcium changes in response to treatment may be expected to occur most rapidly in regions of trabecular bone. The distal end of the radius and the carpals in the hand are mainly trabecular bone as is the os calcis. The os calcis, however, has been shown to lose calcium during periods of bed-rest, a complication which may affect any study being performed over a

long time interval.

- (d) Quantity of overlying soft tissue. Induced activation of elements such as ^{38}Cl and particularly ^{24}Na will interfere with the measurement of ^{49}Ca . The hand and foot have the least overlying soft tissue but not a great deal less than the forearm, which in turn generally has much less than the lower leg.
- (e) Likelihood of changes in the bone structure. Changes in bone shape due to accidents etc., are probably more likely to occur in the foot and hand.
- (f) Ease of positioning. For both irradiation and counting, the region must be completely immobile in a comfortable position for the patient. It was thought that this could more easily be achieved in the case of the forearm which could be strapped into an arm-shaped mould with little discomfort for the subject. A region such as the hand would be the most difficult to immobilise.
- (g) Comparison with other techniques. The main test which activation analysis must be compared with is bone densitometry by photon absorption. This test is performed on the radius and as yet no direct comparison has been made between the two methods at the same site.
- (h) Absolute calcium measurements. Although the emphasis

of the work has not been towards absolute calcium determination, it was felt that if the measurements were required to be normalised, then the long bones of the forearm would probably offer the best chance of success.

2.4 Premoderator Thickness

The function of the premoderator is essentially to "slow down" the neutrons and consequently it performs two functions. The first is to increase the thermal neutron flux and the second to reduce the dose, the largest proportion of which would come from fast neutrons. In the techniques available where the patient's hand gripped a tube containing the neutron source (Catto et al 1973a, Guey et al 1976), the thickness of premoderator was chosen to give the maximum thermal flux. In the first case the dose was fairly high, around 15 rem for each measurement. In our design of the irradiation apparatus the premoderator thickness was chosen not to maximise the thermal flux but to optimise the value of calcium counts per unit dose to the bone.

Gold foils were used to measure the thermal flux. The foils were each approximately 1 cm in diameter and 0.0025 cm thick and weighed about 40 mg. The foils were made from a sheet of gold foil using a cork borer and each one was numbered and weighed. After activation they could be measured easily in an automatic gamma sample counter.

It was not convenient to use Mn, the activation

cross-section of which is similar to calcium, or ^{23}Na , because both these methods would require fairly bulky targets. They are suitable for large sources of a high neutron output, but when a point source 0 to 15 cm away is to be used, their large dimensions would produce errors.

The unavailability of any thermal neutron absorber prevented any correction being made for the epithermal resonances of gold. As the contribution from these would be small and as relative measurements were being performed, it was felt that any error would be minimal.

In addition to thermal flux measurements, the variation in activation of a long bone was simulated using an extended source of NaOH in a perspex tube 30 cm long and 0.8 cm diameter. The induced activity was measured at the centre of a whole body counter by four 15 cm x 10 cm NaI detectors.

The variation in activation and dose with different thicknesses of perspex premoderator is shown in Figure 2.3. By combining the extended sodium source curve with the dose curve (see Section 2.6) in Figure 2.3, curve (1) was obtained in Figure 2.4, which represents the dose per unit activation. It can be seen that there is no minimum on this curve, though the decrease in slope begins to get less with more than 9 cm premoderator. These low values of dose per unit activation, however, could only be achieved with longer irradiation times and with induced activities which have a half life much greater than the

Figure 2.3

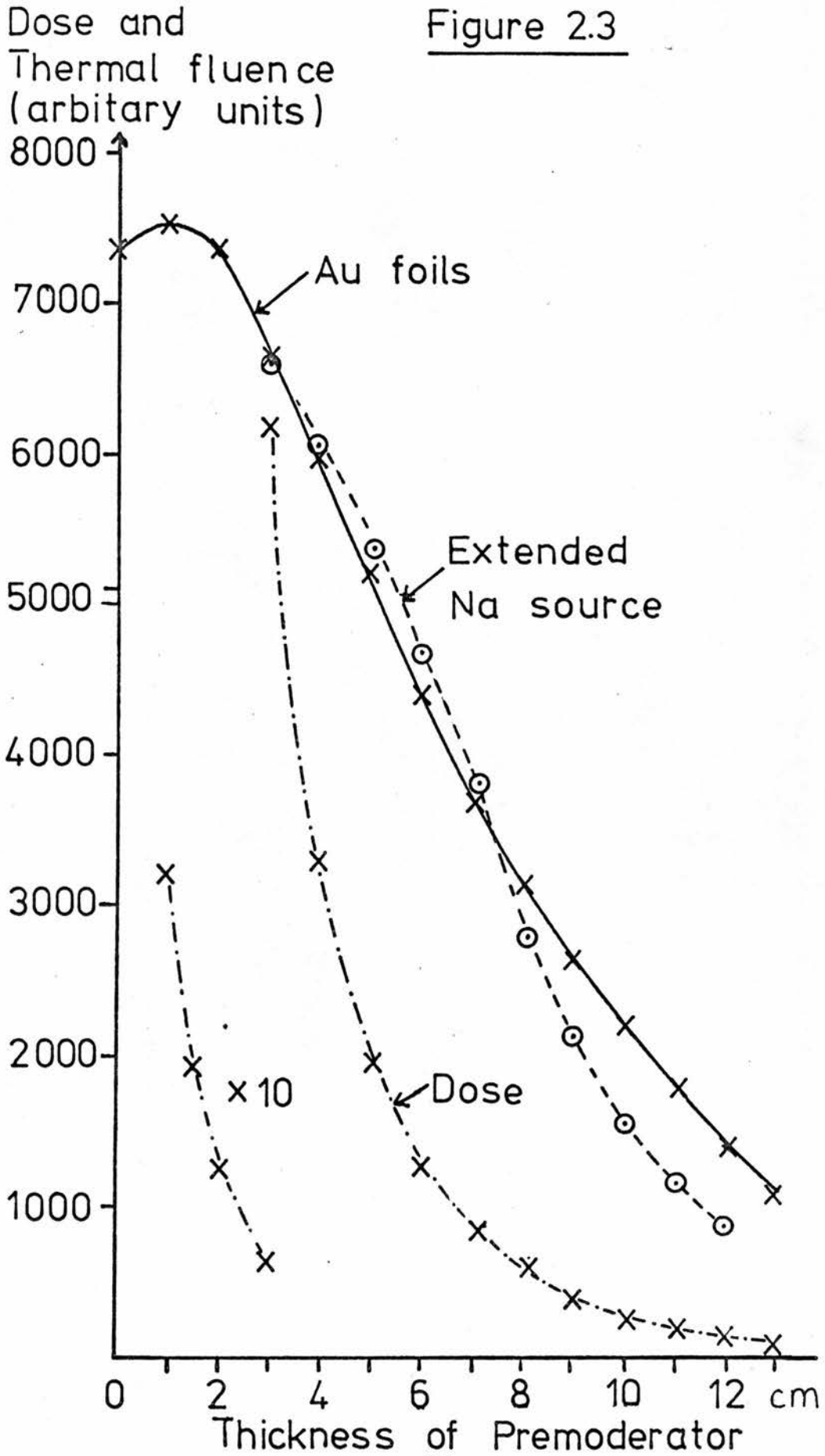
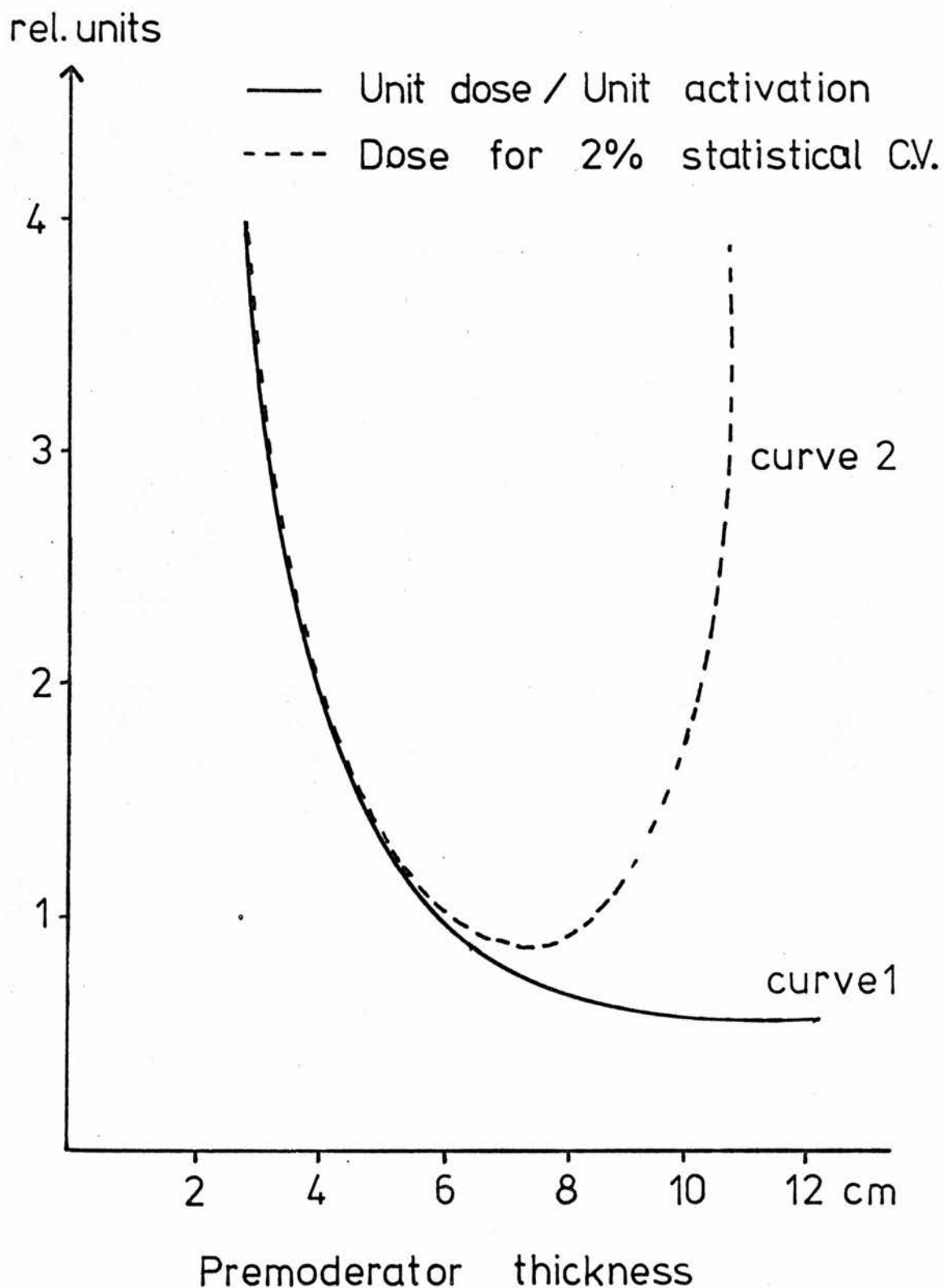


Figure 2.4 Optimal Premoderator
Thickness



irradiation time.

Using the available ^{252}Cf sources the irradiation time was comparable to the half life of the induced ^{49}Ca , and hence the small values of dose per unit activation in curve (1) (Fig. 2.4), could not be achieved.

With 8 cm of premoderator, experiments using a skeletal arm showed that during a 10 min irradiation sufficient counts could be obtained (approximately 5000 to 3000 over a 2 year period). Using this information, the irradiation time required to obtain the same number of counts with different premoderator thicknesses was calculated. The dose per fixed count was then calculated and is shown plotted against the different premoderator thicknesses in curve (2) in Figure 2.4. From this, the optimum premoderator thickness, for the available ^{252}Cf source strength, was found to be about 7.5 cm.

2.5 Patient Irradiation Apparatus

In the design of the irradiation apparatus the limb and the sources had to be surrounded by a form of reflector to increase the thermal fluence through the patient's limb. A hydrogenous material such as paraffin wax or water was most suitable and in addition to reflecting some of the neutrons back through the limb, it also acted as a shield for the more sensitive regions of the patient. Hydrogenous reflecting material was also required around the limb with the available low strength ^{252}Cf sources, to increase the thermal flux through the bone. Tests

showed that about 9 cm of reflector was the minimum thickness required above the limb to give maximum reflection, though in practice more would be desirable to reduce the dose to the rest of the patient.

For the main studies to be performed on the forearm, two different irradiation geometries were used. The first irradiation geometry, geometry A, was used on patients undergoing chronic haemodialysis, the first large patient group to be studied.

In the design of the apparatus for measuring this patient group, consideration had to be given to possible problems that were characteristic to patients on dialysis. The first was the risk of infection from hepatitis. Several of the patients in the study had survived the hepatitis outbreak in Edinburgh in the early seventies and so could have hepatitis antigens. As it was proposed to measure the forearm containing the shunt, as well as the other arm, it was felt that immersion in a water bath, a possible method of moderating and reflecting the neutrons, would be undesirable. Any such water bath would contain a fairly large volume of water and the logistics of performing a large number of patient measurements made changing the water and sterilising the bath not feasible. The second problem was that swellings in the shunt arm could occur. Any such swellings would usually occur at the site where the needles were inserted, so room was left between the arm and the reflector to allow for any such eventuality.

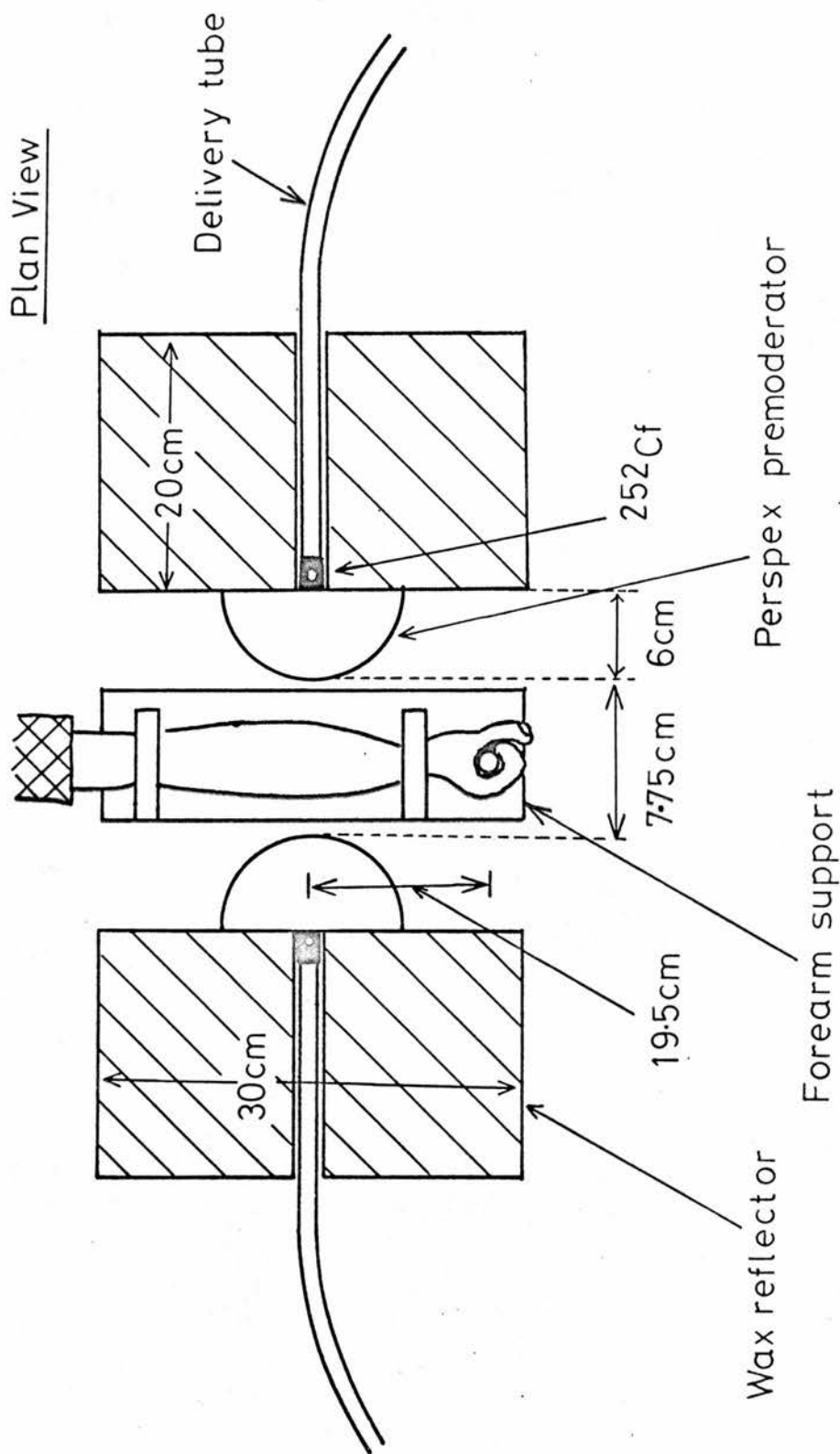
The apparatus for irradiating the forearms of the renal patients is shown in Figure 2.5. The source delivery tubes were positioned inside 30 cm diameter by 20 cm deep cylindrical wax reflectors. Attached to the cylindrical wax reflectors were perspex premoderators. As 7.5 cm had been found to be about the optimum thickness of moderator, semi-cylindrical premoderators of radius 6 cm were used, allowing for an overlying soft tissue thickness of 1.5 cm.

The forearm rested on a perspex support and was positioned using a hand grip and canvas straps with "velcro" fasteners. The forearm support was attached to a wax reflector block 29 cm long, 16 cm wide and 28 cm high below the arm. Above the arm, resting on the tops of the premoderators, was another wax reflector block 30 cm long, 19 cm wide and 12 cm high.

Both of the source/premoderator/reflector assemblies could move with respect to the forearm support and thus the centre of irradiation and the separation between the premoderators could be varied. In actual fact a separation distance of 7.75 cm between the premoderators was used throughout with the centre of irradiation a distance of 19.5 cm from the centre of the hand grip.

In Figure 6.1a the apparatus can be seen with a subject's arm in place, the upper wax reflector being removed for the purpose of the photograph. The subject sat on an adjustable chair in a comfortable position with the arm horizontal from the shoulder. In such a position the patient was unlikely to move and the rest of the body was at least 60 cm from the sources.

Figure 2.5



Irradiation geometry A used for renal patients

The region of bone that was activated and the variation along and across the bone is shown in Figures 2.6 and 2.7. To measure this, gold foils were positioned in an arm phantom 33.5 cm long, 7.5 cm high and 4.5 cm wide made from perspex. The full width at half maximum (F.W.H.M.) of the thermal fluence was 21.6 cm and the variation across the central 5 cm was $\pm 33\%$ at the centre.

In September 1976, measurements were started on more patient groups in addition to the renal patients. By this time the total ^{252}Cf activity was 66 mCi and to increase the activation of ^{48}Ca in the forearm, a new irradiation geometry, geometry B, was designed and constructed.

The cylindrical wax reflectors, into which the delivery tubes went, were still used. However, the perspex premoderators and the upper and lower wax reflectors were replaced by a large water bath (Figs. 2.8, 6.1b). The tank was made of 1 cm thick perspex and the outer width was 17.0 cm. The water acted as a combined pre-moderator and reflector, the neutrons being moderated by about 7.5 cm of perspex/water/soft tissue before reaching the bone. The forearm rest was constructed diagonally at an angle of 45 degrees and the arm was held rigid using a mould of butyrate, the material used for radiotherapy moulds, and a perspex hand grip. The forearm mould was sufficiently elastic to fit any size of forearm, and "velcro" fasteners prevented any vertical movement. An

Figure 2.6

Thermal flux along arm
for both irradiation geometries

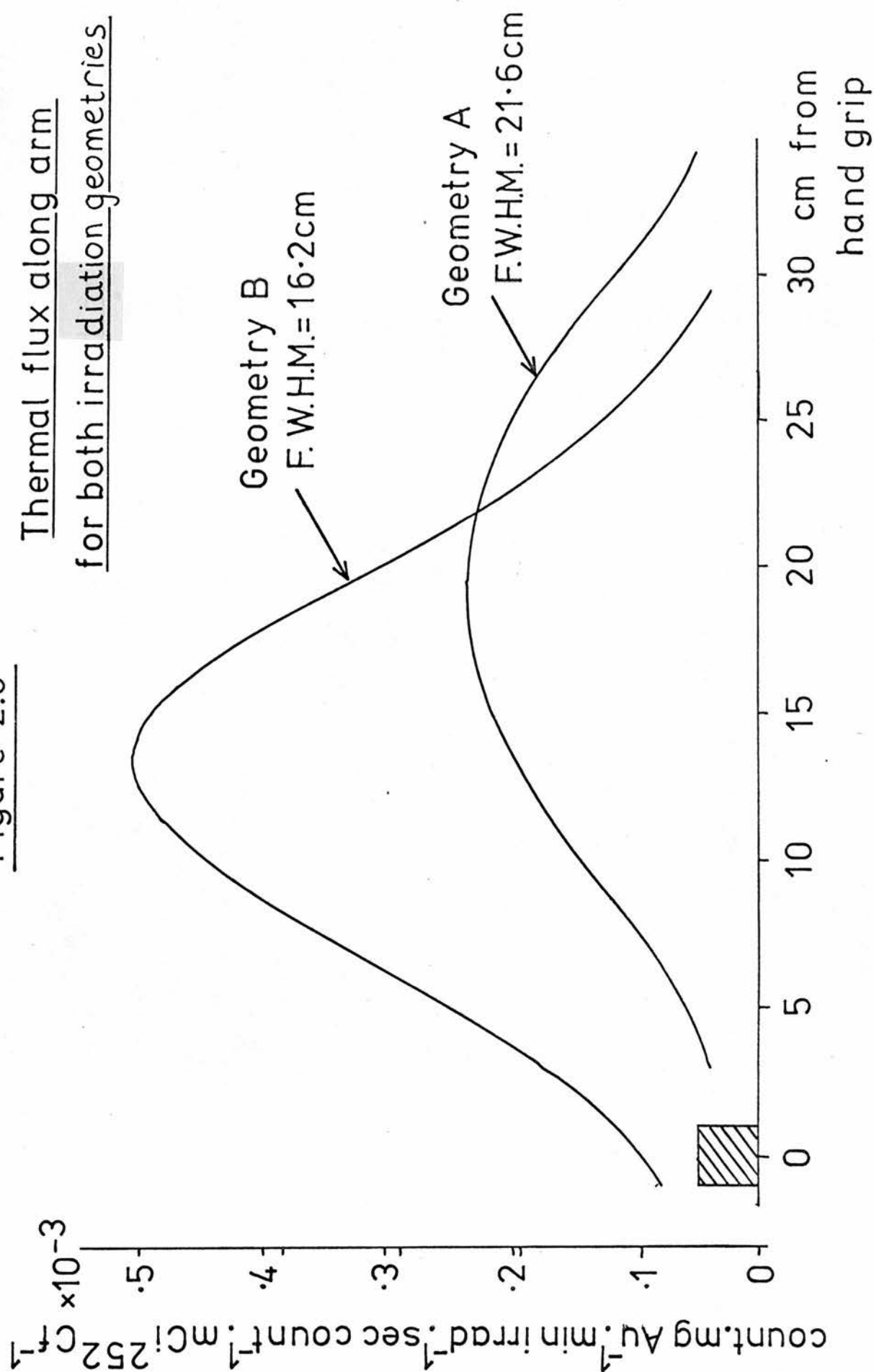


Figure 2.7

Variation in thermal flux across the central

5cm region

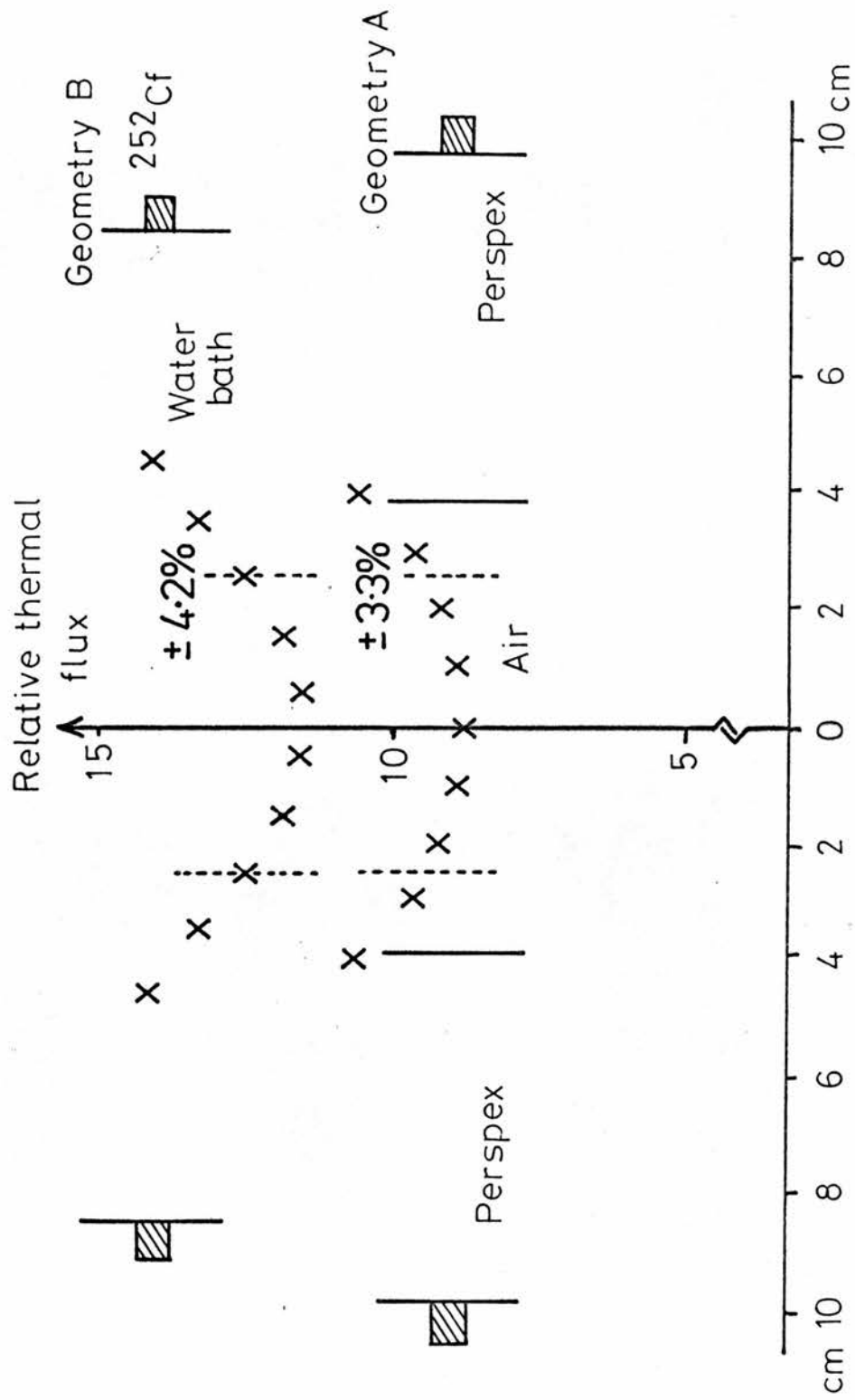
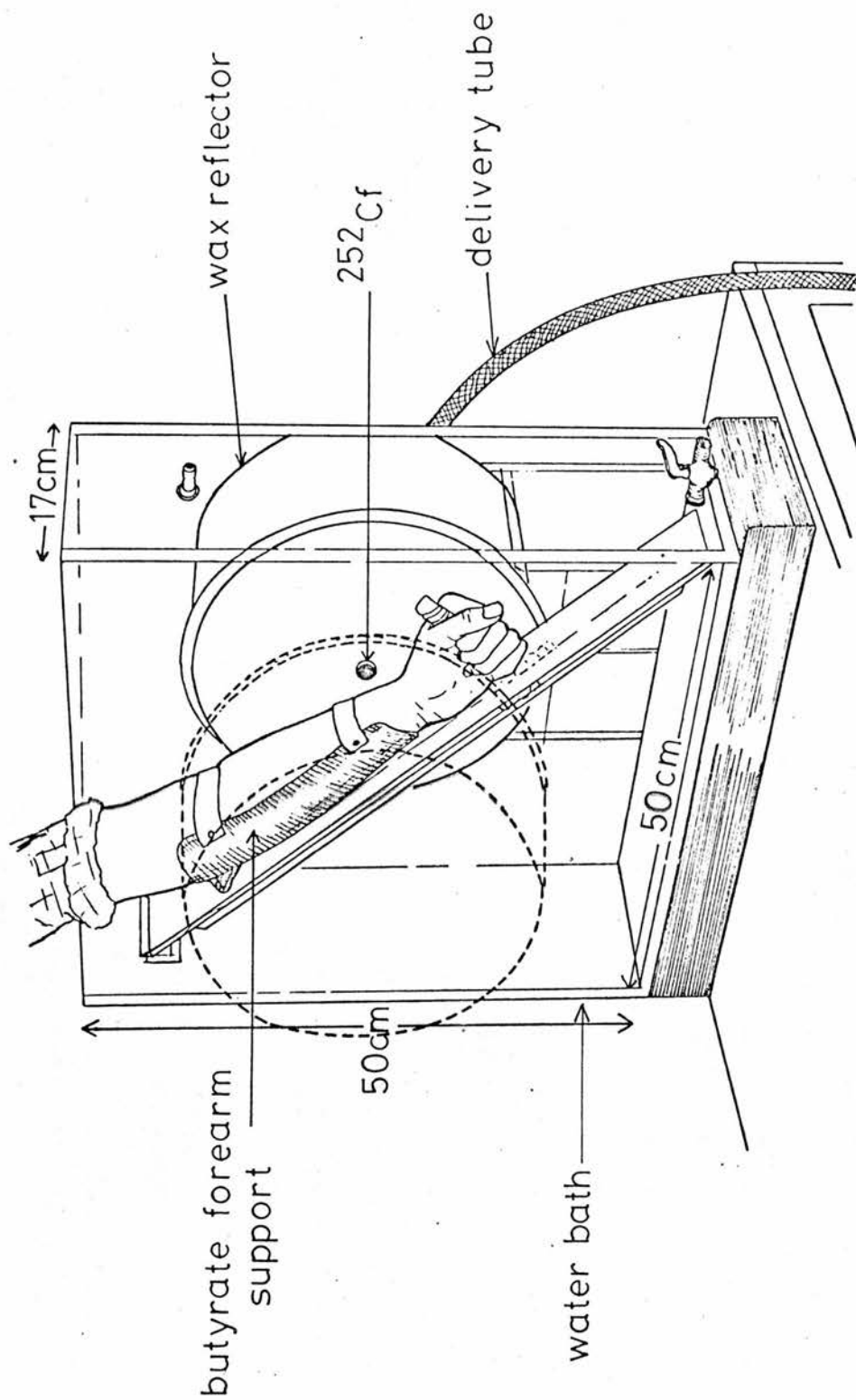


Figure 2.8



Irradiation geometry B

immersion heater could be fixed to a crosspiece at the top of the tank and this was used for a short time each morning to slightly warm the water. Savlon was used in the water as an antiseptic and the water was regularly changed each week.

It was hoped that the elimination of any air gap around the forearm would not only increase the sensitivity of calcium activation but would also eliminate the variation in activation from patient to patient caused by differing amounts of soft tissue as was found in the renal patients. This would be important if at any stage it was decided to try and obtain absolute levels of the bone calcium.

The variation of thermal fluence was measured the same way as for the other irradiation geometry and the curves of variation along and across the bone are shown in Figures 2.6 and 2.7. The F.W.H.M. was less using the water bath, 16.2 cm, than with the first irradiation geometry due to the ^{252}Cf being closer together, (17 cm separation as opposed to 19.75 cm). The sensitivity of activation of irradiation geometry B over the central 25 cm region was an improvement over geometry A by a factor of 1.8.

2.6 Dosimetry Measurements

The dose received by patients was determined experimentally using apparatus that was kindly loan by Dr. R. Lawson and Dr. D. Porter from the Department of Clinical

Physics and Bioengineering in Glasgow. The experiments were performed in early April 1975 when the source activities were each approximately 48 mCi.

The neutron plus gamma dose was obtained using gas flow polythene-ethylene ionization chambers, one being cylindrical and one a parallel plate device. The cylindrical chamber, diameter 1 cm and length 1.7 cm, is described in a N.P.L. report (1974) and is based on a design by Greene (1971). This was used for the principal dose measurements at the position of the bone. The parallel plate chamber (Law et al 1974) was used to measure the dose to the gonads and to the eyes.

The gamma dose measurements were made using a Geiger counter surrounded by graded absorbers to flatten its response to low energy photons (Wagner and Hurst 1961) and also ^{10}B plates to remove thermal neutrons which would have had an effect on the dosimeter. The dimensions of the working end of the Geiger counter were 2.5 cm long and 1.6 cm diameter.

The dose was calculated at the centre of a water-filled cylindrical phantom 7.75 cm in diameter with a source separation of 25 cm and 6 cm premoderation. Ethylene was slowly passed through the ionization chamber and the charge was measured. The chambers had been calibrated previously using a ^{60}Co therapy set so the neutron dose was calculated from the following equation:-

$$D_n(t) = q \times \frac{D_c(t)}{q_c} \times \frac{F_n}{F_c} \times \frac{W_n}{W_c} \times \frac{K_n}{K_c} \times \frac{S_n}{S_c} - D_\gamma(t)$$

where t refers to tissue, c cobalt and n neutrons. After calculating the kerma ratios, the total dose to the bone could be expressed in rads. Further explanation of this equation and other mathematical details are given in Appendix I.

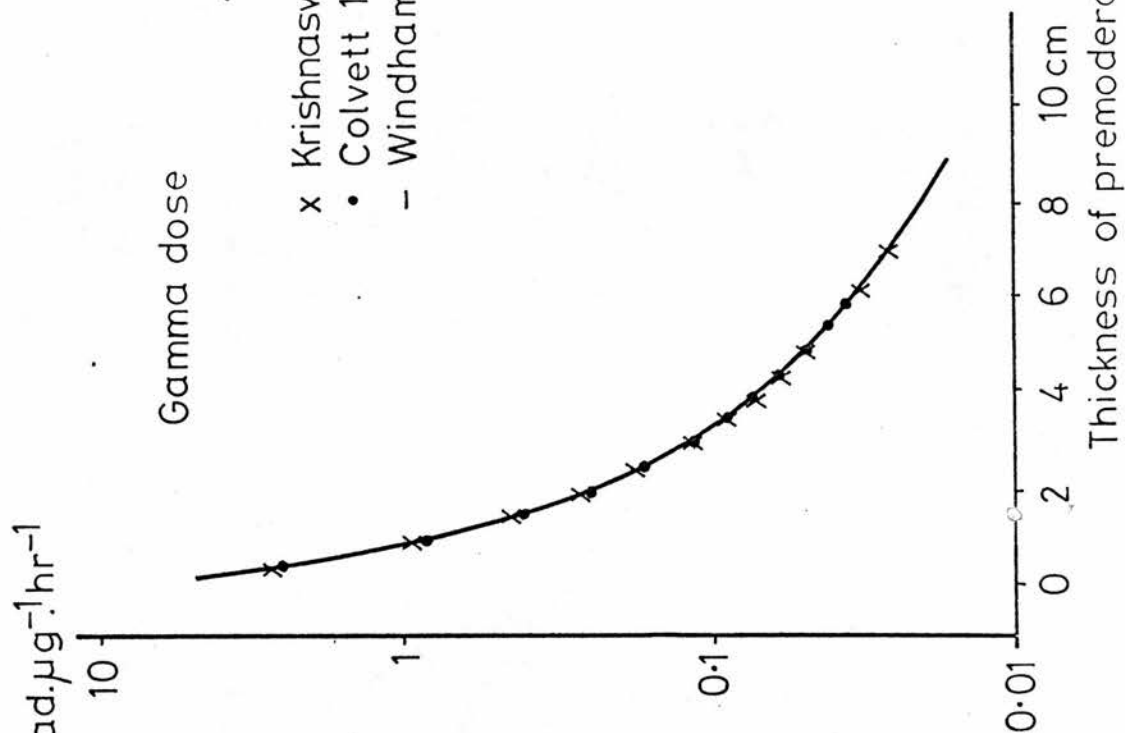
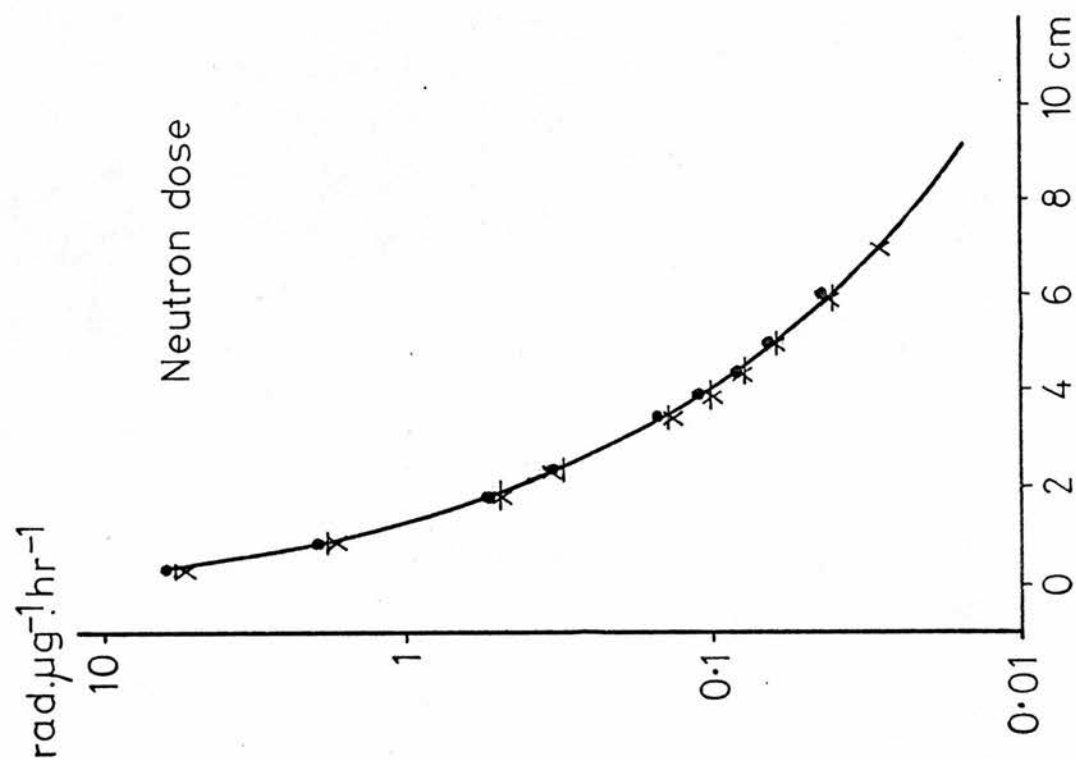
The gamma dose in rads was obtained by combining the calculated ^{252}Cf gamma spectrum at the centre of the water phantom with the response of the geiger counter with energy. Thus, after including a correction for dead time, a value for rad.count^{-1} was obtained.

The results of the dosimetry measurements at the position of the bone were $0.0185 \text{ rad.min}^{-1}$ from neutrons and $0.0177 \text{ rad.min}^{-1}$ from gamma radiation. From these figures the dose to the bone in rad.min^{-1} was calculated for the two forearm irradiation geometries A and B which had source separation distances of 19.75 cm and 17 cm respectively. The dose to the skin was estimated using the data in Figure 2.9 (Krishnaswamy 1972, Colvett et al 1972, Windham et al 1972), assuming a tissue thickness of 2.5 cm.

To calculate the dose in rems to the skin surface and to the bone, the mean R.B.E. was calculated for a californium spectrum after 6 cm and 8.5 cm premoderation. The californium spectrum at intervals of 1 cm was calculated from the original spectrum (Amersham 1972) using the equation:-

$$nv = (nv_o) e^{-(N_H \sigma_H + N_o \sigma_o + N_c \sigma_c) x}$$

Figure 2.9



where v = neutron energy

N = no. of atoms of hydrogen, oxygen or carbon

σ = total neutron cross-section at neutron energy v_0

x = distance through premoderator

the values of the total neutron cross-sections at different energies given by Hughes and Harvey (1955). The spectra at 6 cm and 8.5 cm were then combined with the variation of R.B.E. with energy (N.C.R.P. 1971) using the equation:-

$$\overline{\text{R.B.E.}} = \frac{\sum \text{R.B.E.}(E) \times n(E)}{\sum n(E)}$$

where n is the number of neutrons at energy E . The mean R.B.E. after 6 cm and 8.5 cm premoderation was found to be 7.75 and 5.89 respectively.

The doses to the skin and bone for a total source strength of 96 mCi are given in Table 2.1. The dose averaged over the forearm, given during a single measurement of a patient during the period of the clinical studies, is shown in Figure 2.10.

With a total source strength of 96 mCi the dose to the gonads and eyes was less than $0.002 \text{ rem.min}^{-1}$ using a quality factor of 10 for neutrons.

Figure 2.10

Dose to patients averaged over the forearm

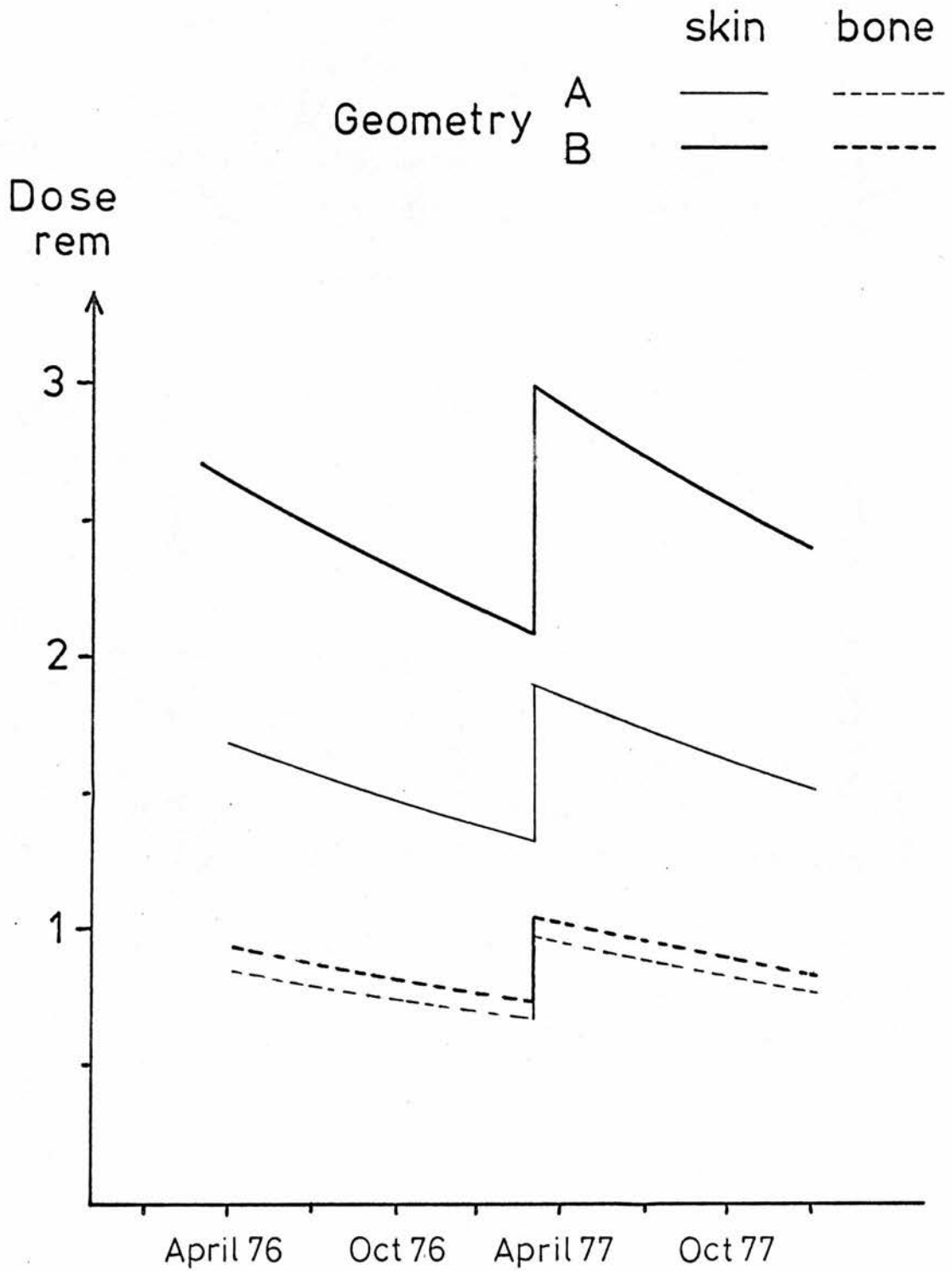


TABLE 2.1					
Total Source Strength 96 mCi (April 1975)					
		Peak Dose (rem.min ⁻¹)			Total dose averaged over the forearm (rem.min ⁻¹)
		neutron	gamma	total	
A	{ Bone	0.179	0.029	0.208	0.112
	{ Skin	0.489	0.056	0.545	0.218
B	{ Bone	0.235	0.038	0.273	0.121
	{ Skin	0.775	0.088	0.863	0.344

Two other methods were investigated to measure the neutron dose but both proved unsuitable because of the low dose rate. The first was the use of discs of FeSO_4 solution which were the same size as the parallel plate ionization chamber. Experiments were performed with the sources separated by 24 cm, a 6 cm premoderator in front of each and a stack of 12 discs in the middle. The true dose measurement at each disc position was measured with the parallel plate chamber and it was hoped to combine this with the measured changes in optical density of FeSO_4 to calculate the G value for ^{252}Cf . Unfortunately after irradiating the FeSO_4 for 4 days the optical density had only changed from 696 ± 7 to around 925 which did not allow G to be calculated with sufficient accuracy. In addition, even if the G factor were known, subsequent dose measurements would have to be performed over time periods of about 1 week which would be impractical.

The second method to be investigated was the

detection of fast neutron induced fission fragments from ^{237}Np (Cross et al 1975). An attempt was made to measure these using Macrofol polycarbonate foils which were subsequently etched and viewed under a microscope. The density of tracks was so low as to make it unsuitable for such a low source strength.

CHAPTER 3.

CHAPTER 3

DETECTION APPARATUS

3.1 Detectors and Shielding

To measure induced activity at partial body sites, a purpose built counter had to be designed and constructed. Although calcium measurements of the forearm were the dominant interest, the partial body counter was designed to be as versatile as possible to enable it to be used for measurements of the lower leg and thyroid, in addition to the forearm. Also included in the specifications, but not of prime importance, was the ability to measure large urine samples in 2 litre containers and also whole body measurements of small animals such as rats.

The basic design consisted of two NaI(Tl) detectors each mounted inside lead cylinders which were mobile on a large steel table. The two detectors could be used on their own or in conjunction with a large central shield or a thyroid collimator, the latter being bolted onto the front of the table. Bilateral detection was considered to be the best geometry to reduce positional errors.

The detectors used were two Quartz and Silice "Scintiflex 152 YFE 102". The size of the NaI crystal was 15.2 cm x 10.2 cm and the overall length of each detector, crystal plus photomultiplier tube, was 41 cm. The detectors had to be modified slightly to change the position of the potentiometer and input/output socket from

the side of the aluminium casing to an insert in the base, care being taken to keep all joints light tight.

Each detector was enclosed in a lead cylinder which was cast in five sections to follow the outline of the detector as closely as possible (Fig. 3.1). By following closely the contours of the detector, the weight of lead could be kept to a minimum whilst ensuring a thickness of at least 6.5 cm shielding all around the crystal. Although the background at 3.10 MeV (the region of the calcium photopeak) was very low, this thickness of lead was considered necessary to reduce the relatively large background peak at 2.60 MeV from thorium decay products. The lead used in all the shielding was monitored for contamination, whilst in the form of ingots, before it was cast into sections. The lead enclosed detectors were supported on small trollies with wheels at the front, which could easily be manoeuvred using a simple lever jack pivoted on strong wheels.

The central shield, into which the two detectors could be positioned, is shown in Figure 3.2. Again the design was such as to ensure a 6.5 cm thickness of lead around the crystal, excepting the limb entrances. For forearm measurement, the limb was placed inside the central shield on a perspex arm rest with the two detectors either side separated by 9.0 cm. Longitudinal movement of the arm was prevented by means of an adjustable hand grip and transverse movement by means of a butyrate mould shaped to fit closely round the forearm. When not in use the central shield could be wheeled to the back of the table using the

Figure 3.1
Design of shielding for detectors

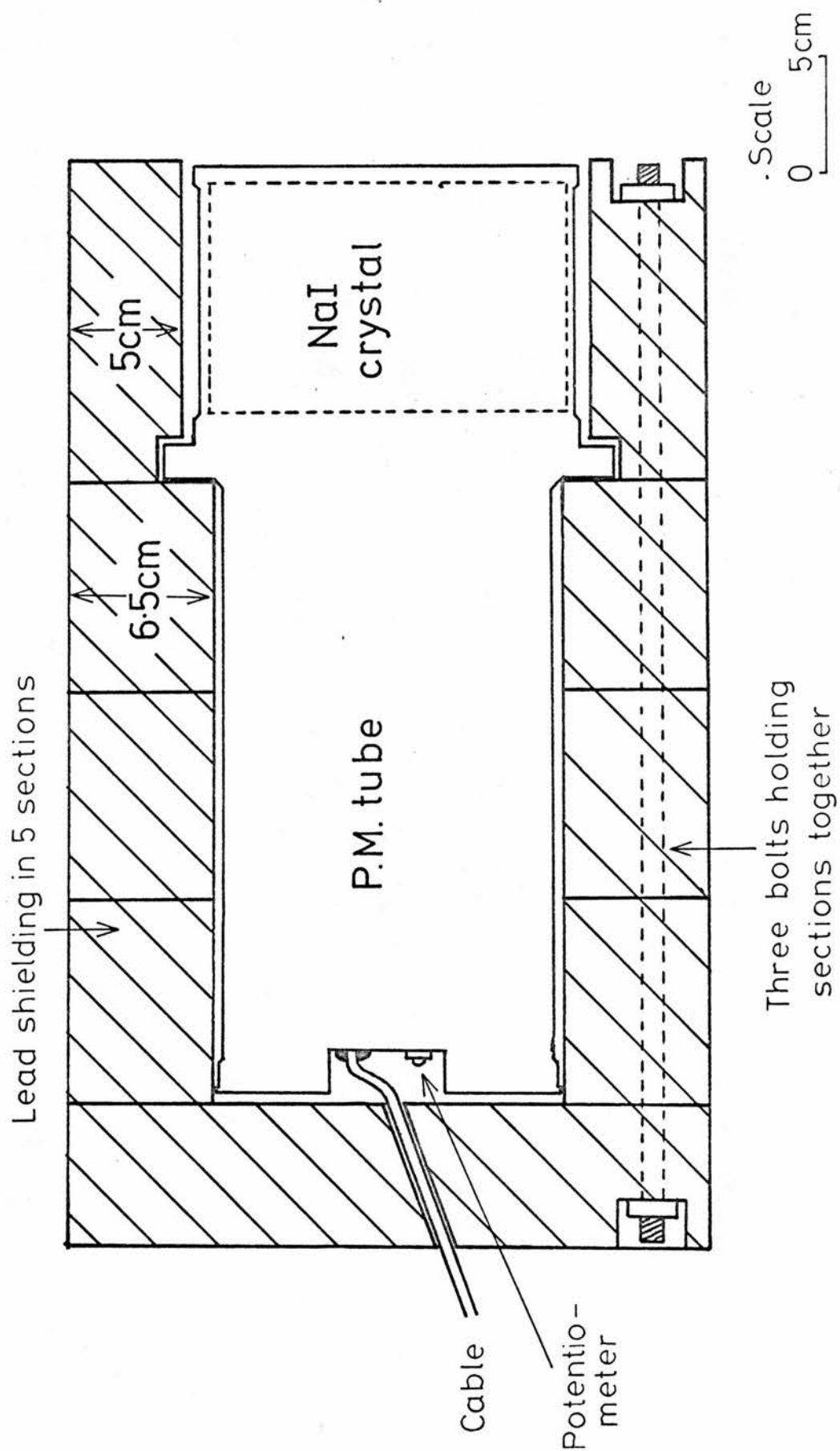
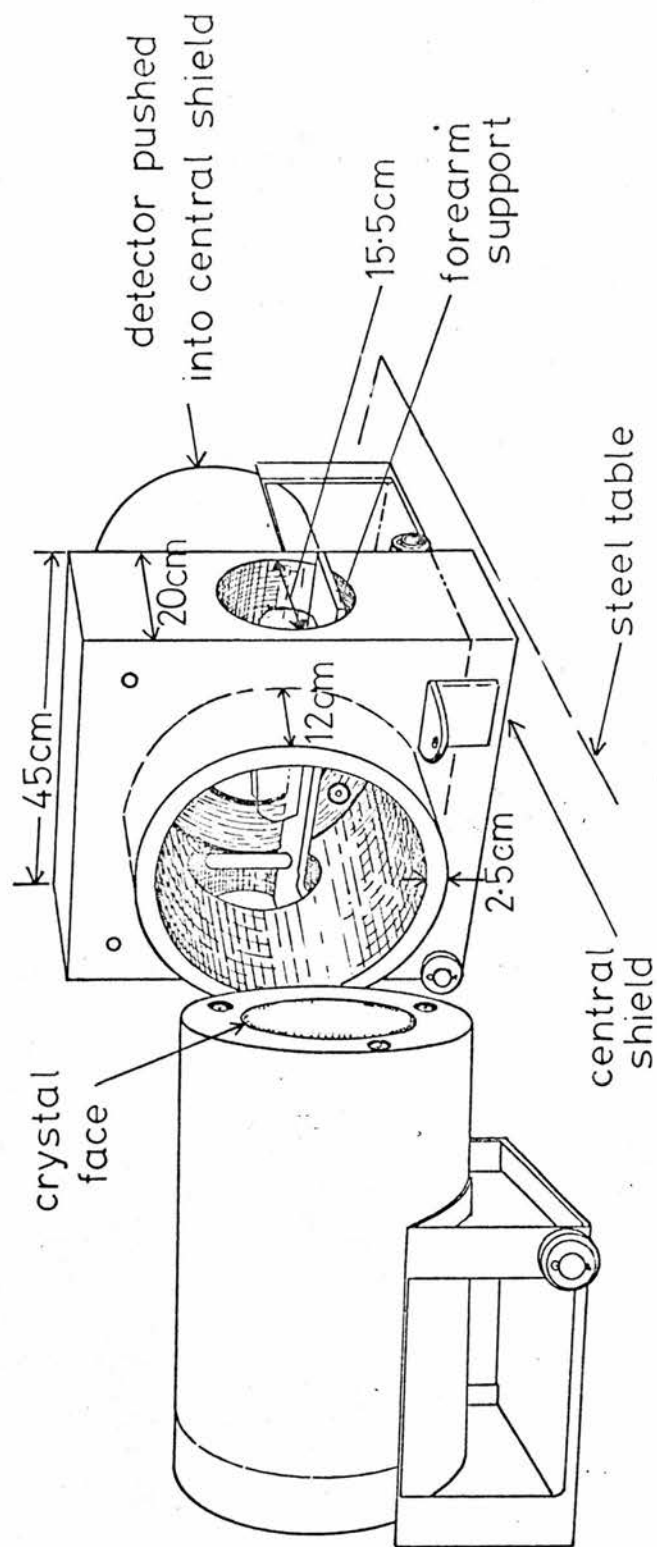


Figure 3.2
Partial body counter with one detector
removed from central shield

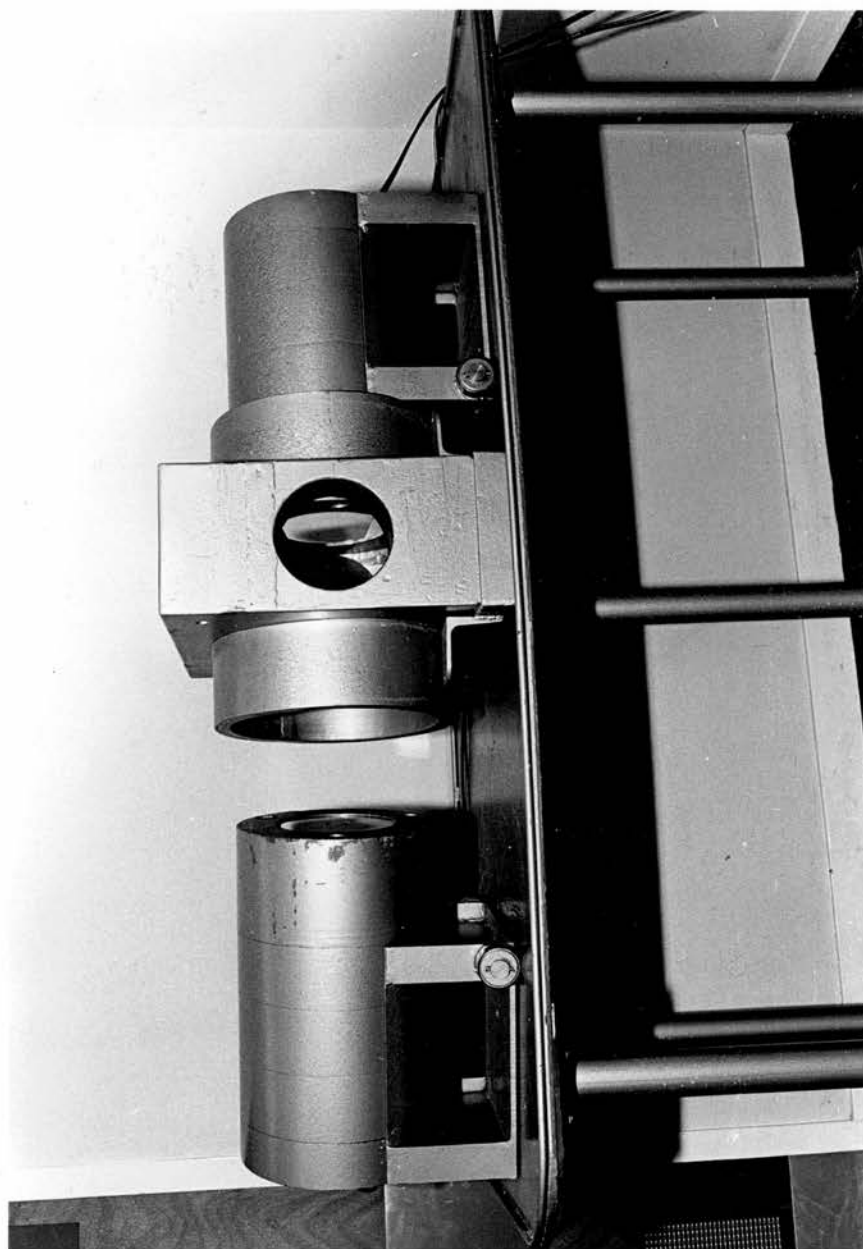


wheeled levers previously described. If the central shield was required for counting large urine samples, the containers could be placed inside through the holes into which the detectors were placed. Whole body rat measurements were also performed with the apparatus using the perspex arm rest but with the plastic arm mould removed. A photograph of the partial body counters is shown in Figure 3.3.

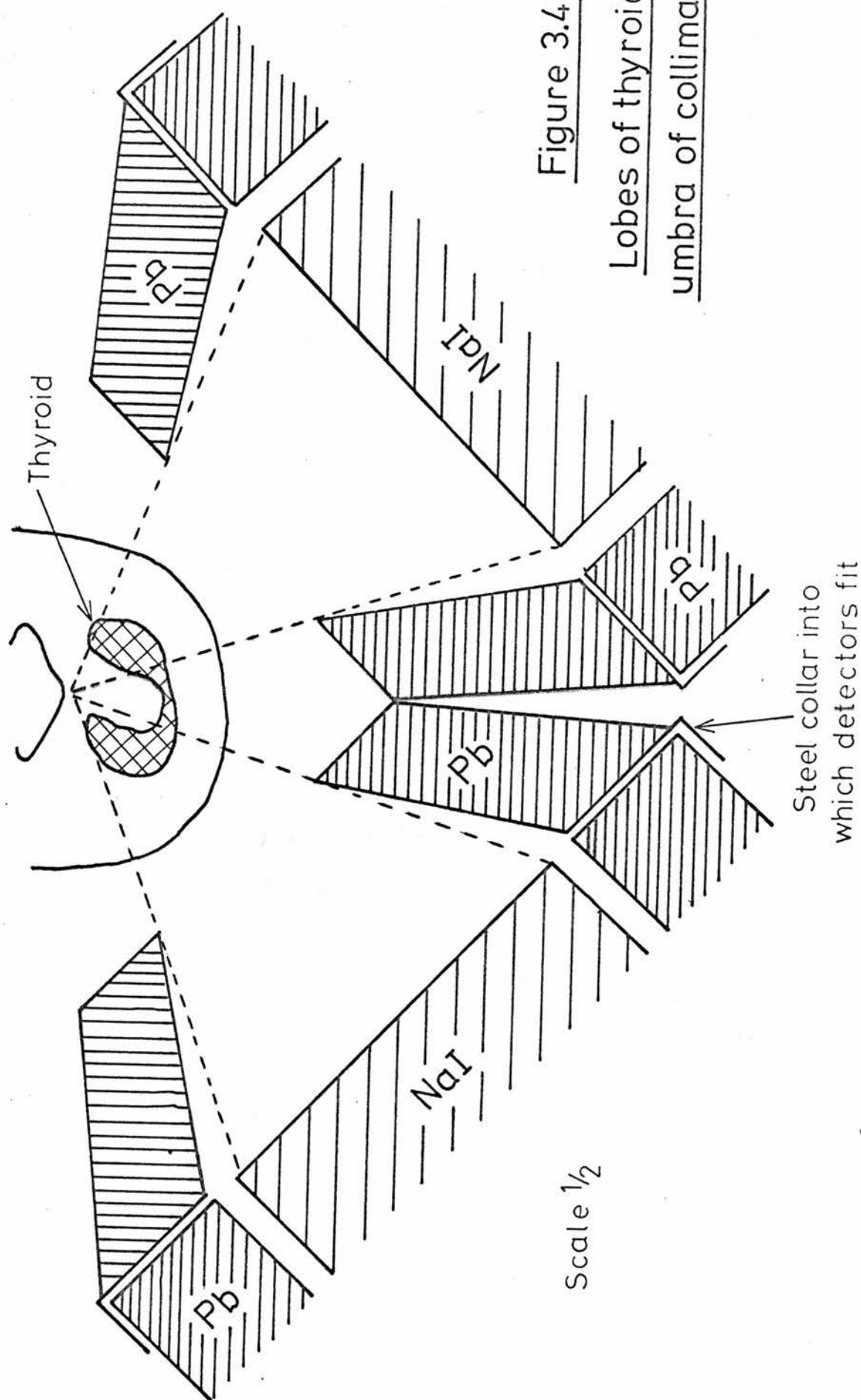
For measurements of the thyroid, a double collimator could be bolted onto the front of the table and the two detectors fitted into it at an angle of 90° (Fig. 3.4). The front of the thyroid collimator extended over the edge of the table so that the patient could easily sit with his neck close to the collimators and without his chest touching the table. The collimator each side was tapered to an outer diameter of 15 cm at the front in order to fit fairly comfortably between the chin and clavicle. The shape of the collimator was designed to reduce the measured activity from regions other than the thyroid. It was proposed to construct a small movable lead wall to place behind the patient's neck but this was not done as thyroidal iodine measurements were found not to be feasible because of the low source strength (Appendix II).

The weight of the lead shielding used in the partial body counter was as follows: each detector shield - 220 kg; the central shield - 310 kg; the thyroid collimator - 50 kg. To support this weight, the table that the detectors moved on was made of half-inch steel plate supported at the four corners and at the centre by tubular steel

FIGURE 3.3



Partial Body Counter.



legs. A small metal bar was welded onto the edge of the table to form a "lip", so preventing any of the apparatus from being wheeled off the table. The dimensions of the table were 182 cm by 91.5 cm and height 84 cm.

3.2 Electronic Equipment

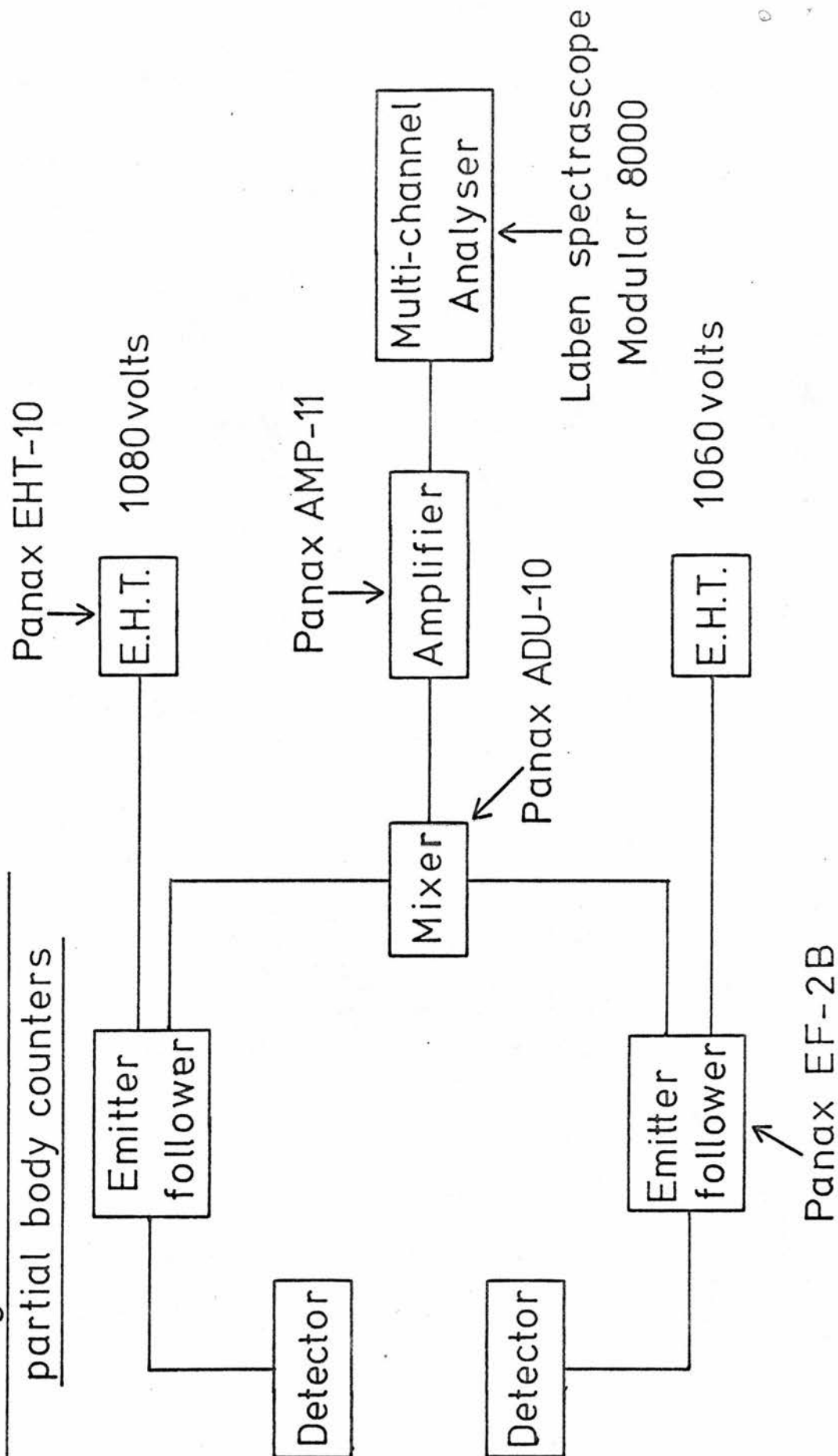
A block diagram of the electronics linked to the two detectors is shown in Figure 3.5. A single cable carried the E.H.T. and signal through the lead shielding, from the photomultiplier assembly to an emitter follower which was attached to the rear of each detector shield to minimise the distance travelled by the combined signals. From each emitter follower two leads were connected to a 'NIM BIN' which contained the E.H.T. supplies, mixer and amplifier. It was found that when the detectors were operated at their recommended voltages, their response was non-linear at energies above 2.5 MeV. This problem was cured by lowering the E.H.T. voltage to around 1050 volts and at this voltage, linearity was achieved up to 3.5 MeV. Having set the voltage, the rear section of the detector shield was removed and the potentiometer adjusted to give optimum resolution for the two detectors at 2.75 MeV.

A consequence of the lowered E.H.T. voltage was the tendency for the gain to vary, i.e. the positions of the peaks would drift. Special care was therefore taken and the detectors were calibrated twice each day using ^{24}Na and ^{60}Co sources.

The signal from the amplifier was fed into a 1024

Figure 3.5

Block diagram of electronics for
partial body counters



channel multichannel analyser. These 1024 channels could be divided into sub-groups and for most measurements the background spectrum was stored in 512 channels and the patient spectrum in the rest. The background could be subtracted from the patient spectrum, integrations performed and an output of the required section of the spectrum obtained on a teletype or paper tape for computer processing.

3.3 Background and Counting Efficiency

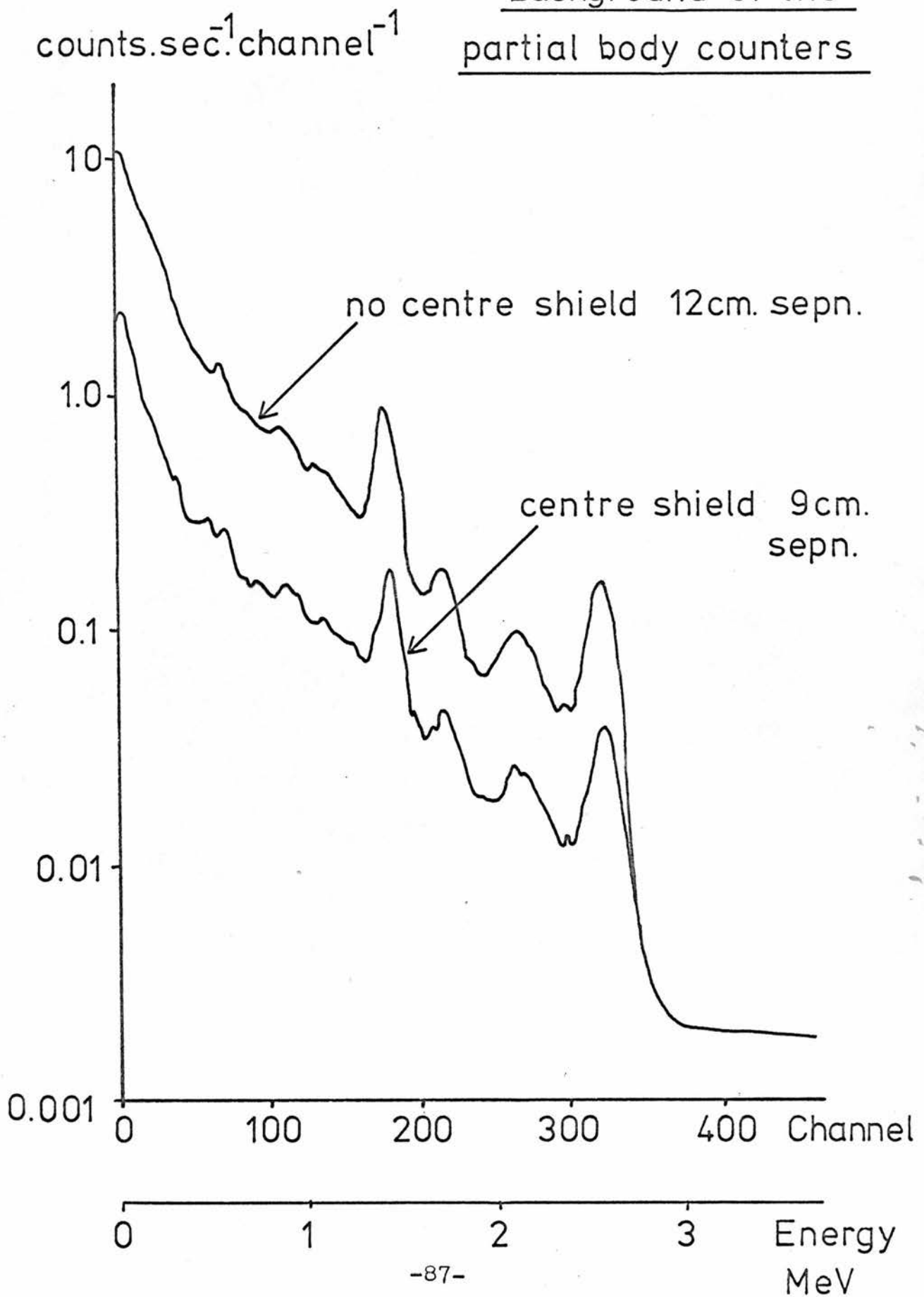
The low activity, and in the case of ^{49}Ca , the short half life of the induced radiation, required the efficiency of measurement to be kept as high as possible while keeping the background low to achieve adequate counting statistics. The background spectra between 0 and 4 MeV are shown in Figure 3.6 for different detector arrangements.

The efficiency of the two detectors in the central shield with 9 cm separation was 31% at 2.75 MeV. The background count rate between 2.9 MeV and 3.3 MeV was approximately 0.09 counts per second (c.p.s.). The background in the calcium photopeak region did not increase greatly if the central shield was removed (0.15 c.p.s., 12 cm separation) but the background peak at 2.6 MeV increased approximately six-fold.

The background peak at 2.60 MeV which would interfere most with calcium measurements was monitored over periods of 1000 sec for 48 hours to test for any variation. Fortunately it was found to be stable, any slight variation

Figure 3.6

Background of the
partial body counters



being purely statistical.

With the thyroid collimators and a lead "shadow shield" wall behind the patient's neck, a background of 5.8 c.p.s. was obtained between 400 KeV and 500 KeV.

3.4 Variations in Counting Sensitivity

To obtain good reproducibility of measurement the variation in counting sensitivity across the region being measured must be kept to a minimum. With bilateral irradiation there was little variation over the central 5 cm; $\pm 6\%$ and $\pm 5.8\%$ with separations of 9 cm and 12 cm (Fig. 3.7). The variation in sensitivity with the central shield along any bone that was measured is shown in Figure 3.8. The F.W.H.M. was 21.8 cm which was similar to the irradiation profile and the product of the curves is shown in Figure 3.9, illustrating the region of the limb that would be measured. Isocount lines for bilateral irradiation with the central shield and for the thyroid collimator are illustrated in Figures 3.10 and 3.11 respectively.

3.5 Optimum Counting Time

The short half life of ^{49}Ca meant that as the detection time was increased, so the percentage contribution to the gross counts in the calcium region from the background increased. Therefore an optimum counting time existed to give the minimum statistical coefficient of variation, for different source strengths and irradiation geometries.

Figure 3.7

Variation in sensitivity between detectors

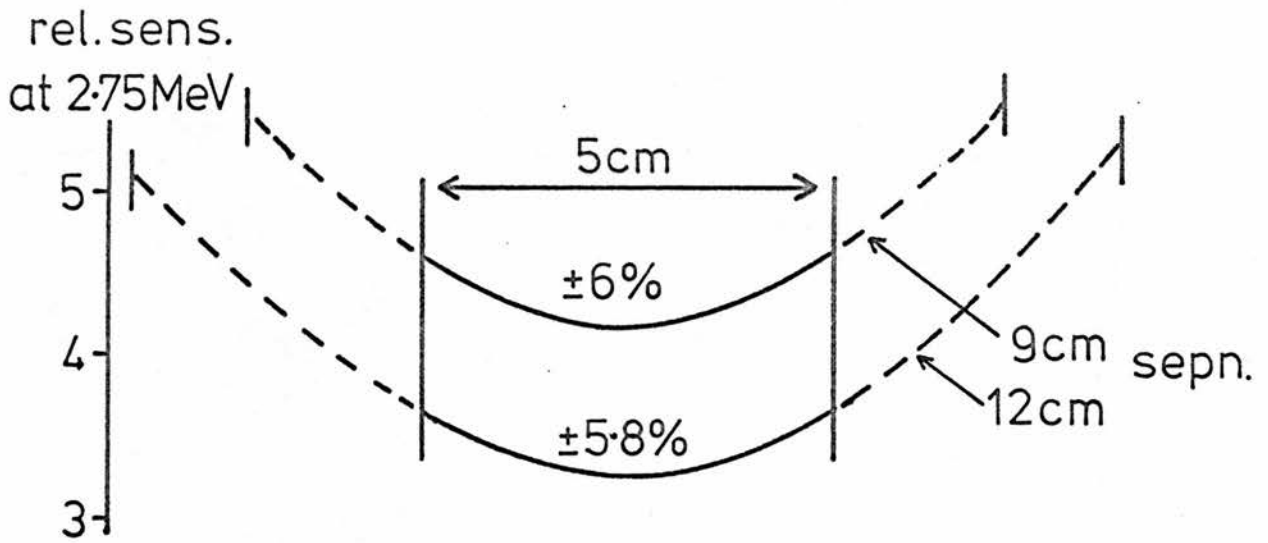


Figure 3.8

Variation in sensitivity along limb

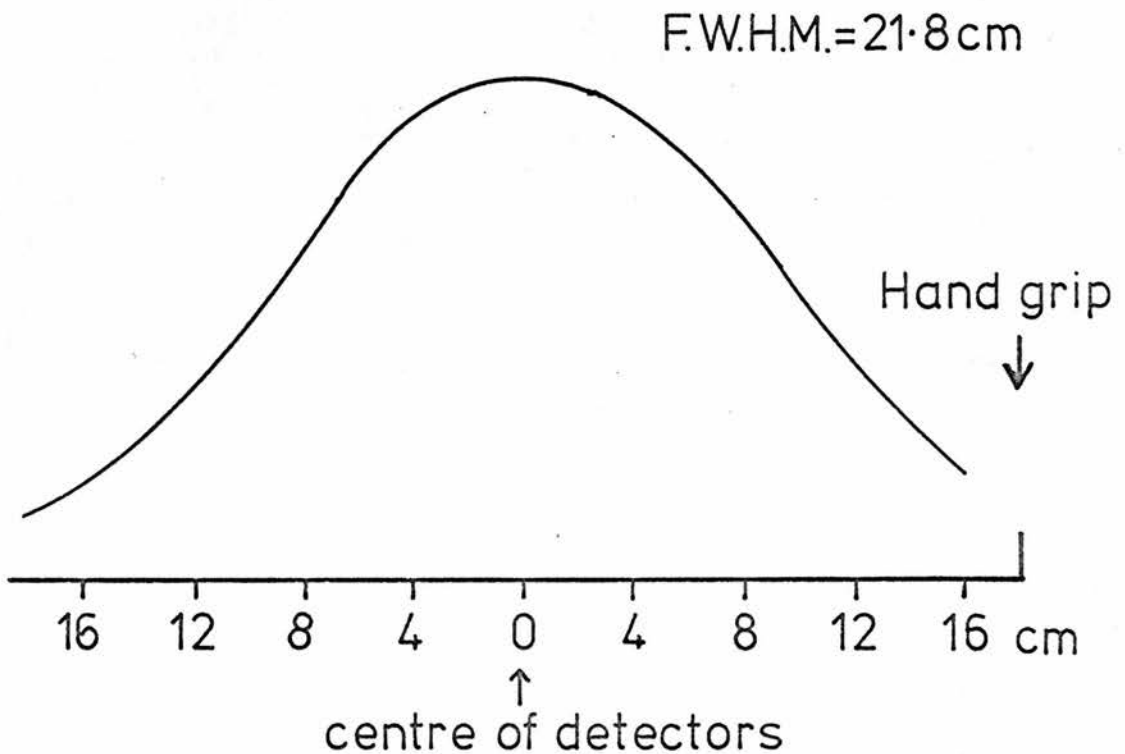


Figure 3.9

Variation in sensitivity of
calcium measurement

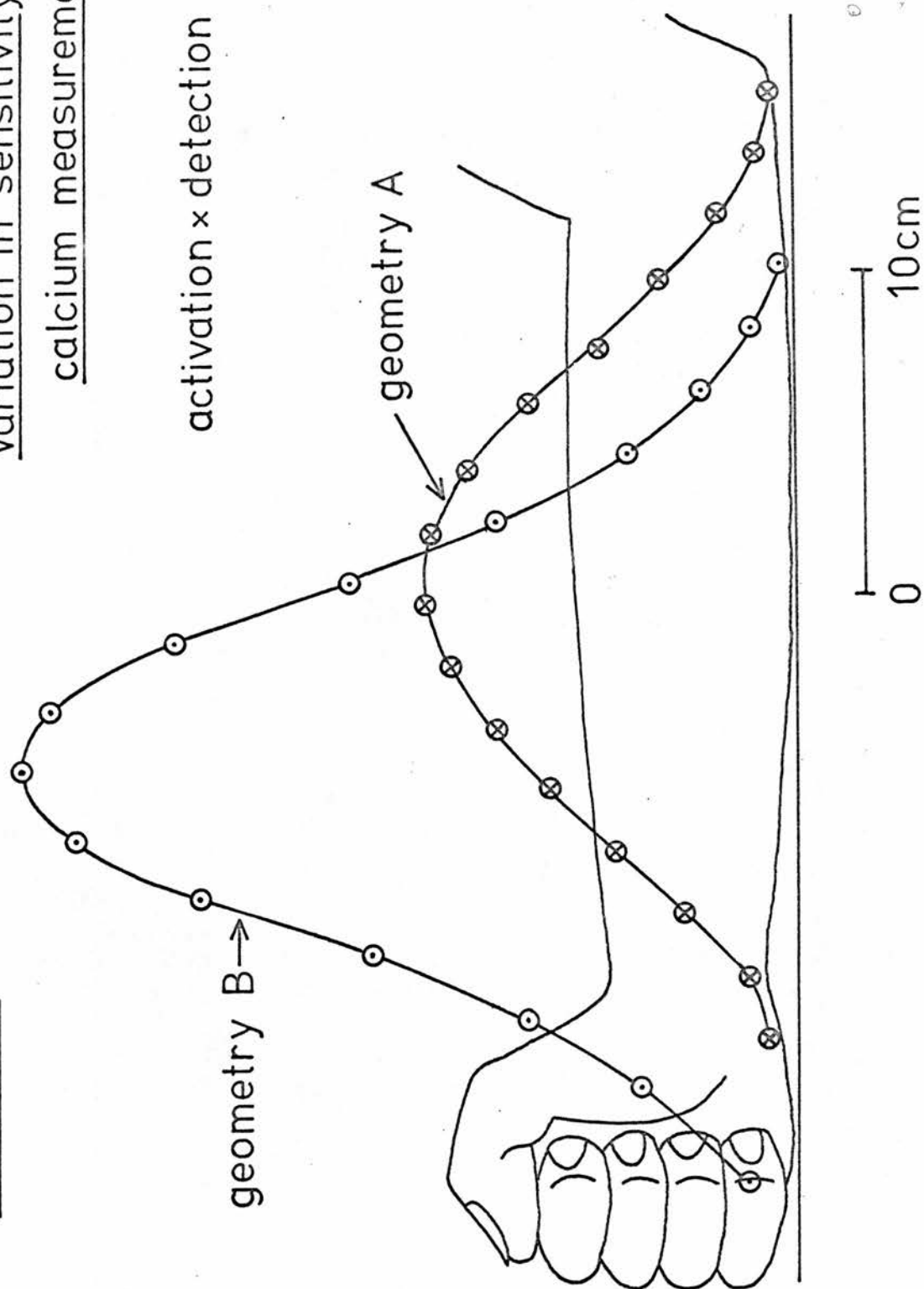


Figure 3.10
Isocount lines - using ^{24}Na

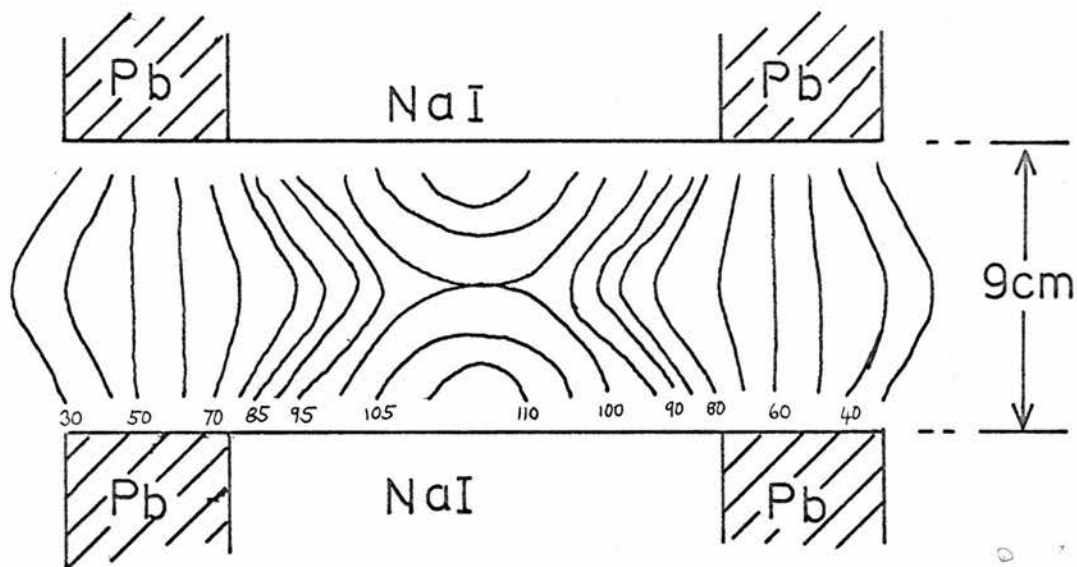


Figure 3.11

Isocount lines
using ^{85}Sr

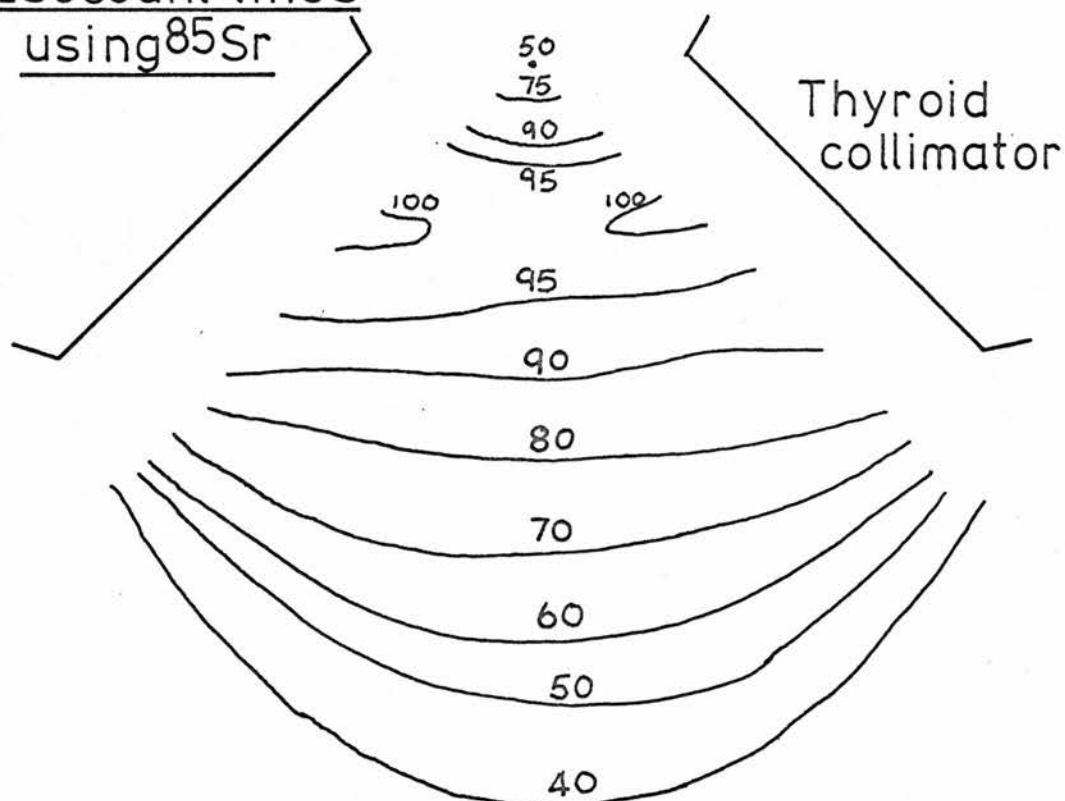
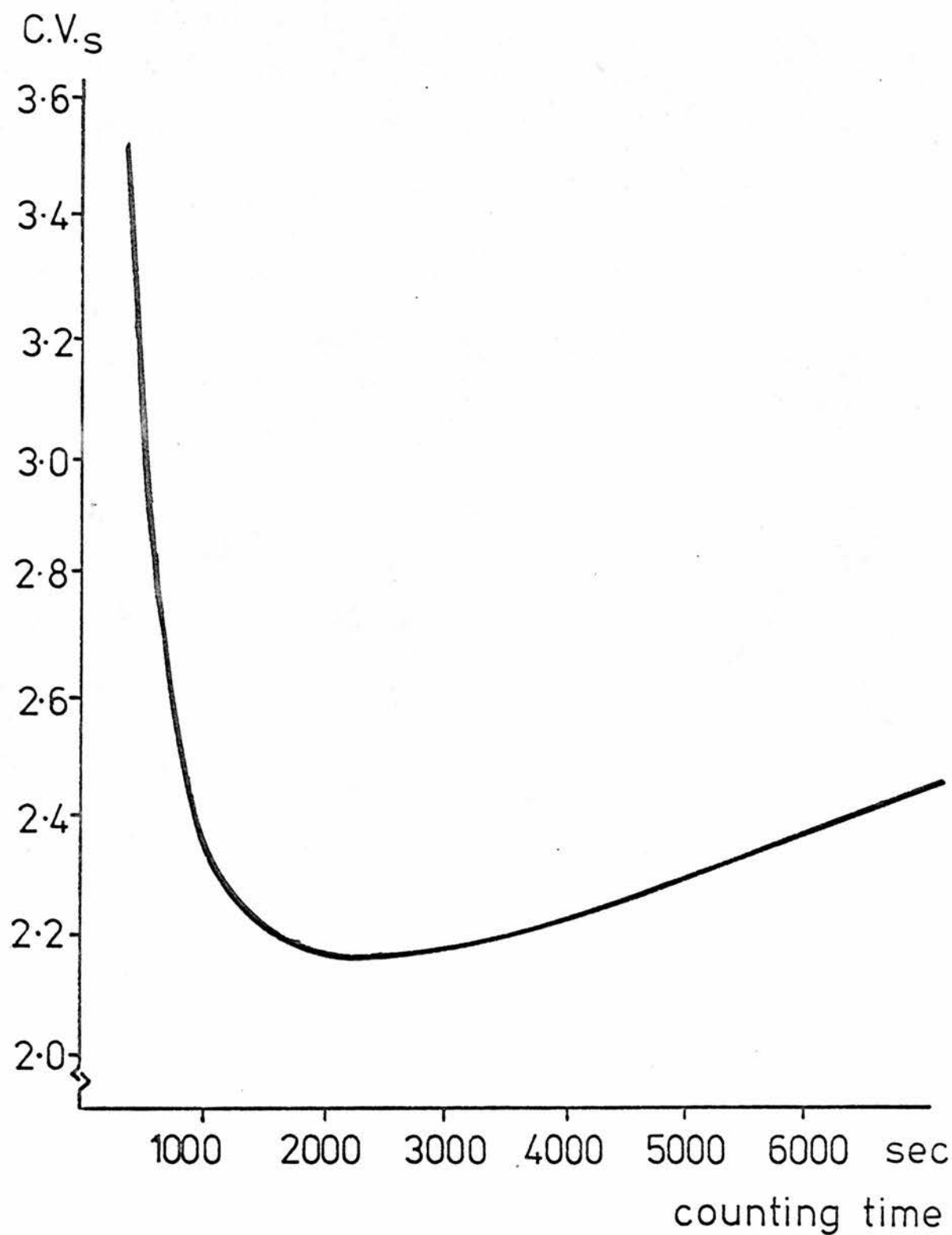


Figure 3.12
Statistical C.V. versus
counting time



CHAPTER 4.

CHAPTER 4

DATA ANALYSIS

4.1 Interference

Having obtained a spectrum of the induced activity, the number of counts due to ^{49}Ca alone must be determined. When performing such an analysis, consideration was given to possible interference from the following sources:

- (a) Counts in the ^{49}Ca photopeak region from the adjacent peaks of ^{38}Cl and ^{24}Na .
- (b) Coincidence peaks at high energies from the much larger photopeaks at lower energies.
- (c) Any ^{37}S produced from the $^{37}\text{Cl}(n,p)^{37}\text{S}$ reaction, which has a peak at 3.1 MeV.

Taking these in the inverse order, there was no possibility of significant interference from ^{37}S using moderated neutrons from ^{252}Cf . ^{37}Cl has a threshold of activation of 3.5 MeV and the very low number of neutrons above this energy that were present after premoderation ensured negligible activation of the ^{37}Cl , even though the product of $\text{atoms} \cdot \text{gm}^{-1} \cdot \sigma_{\text{act}}$ is comparable to ^{48}Ca .

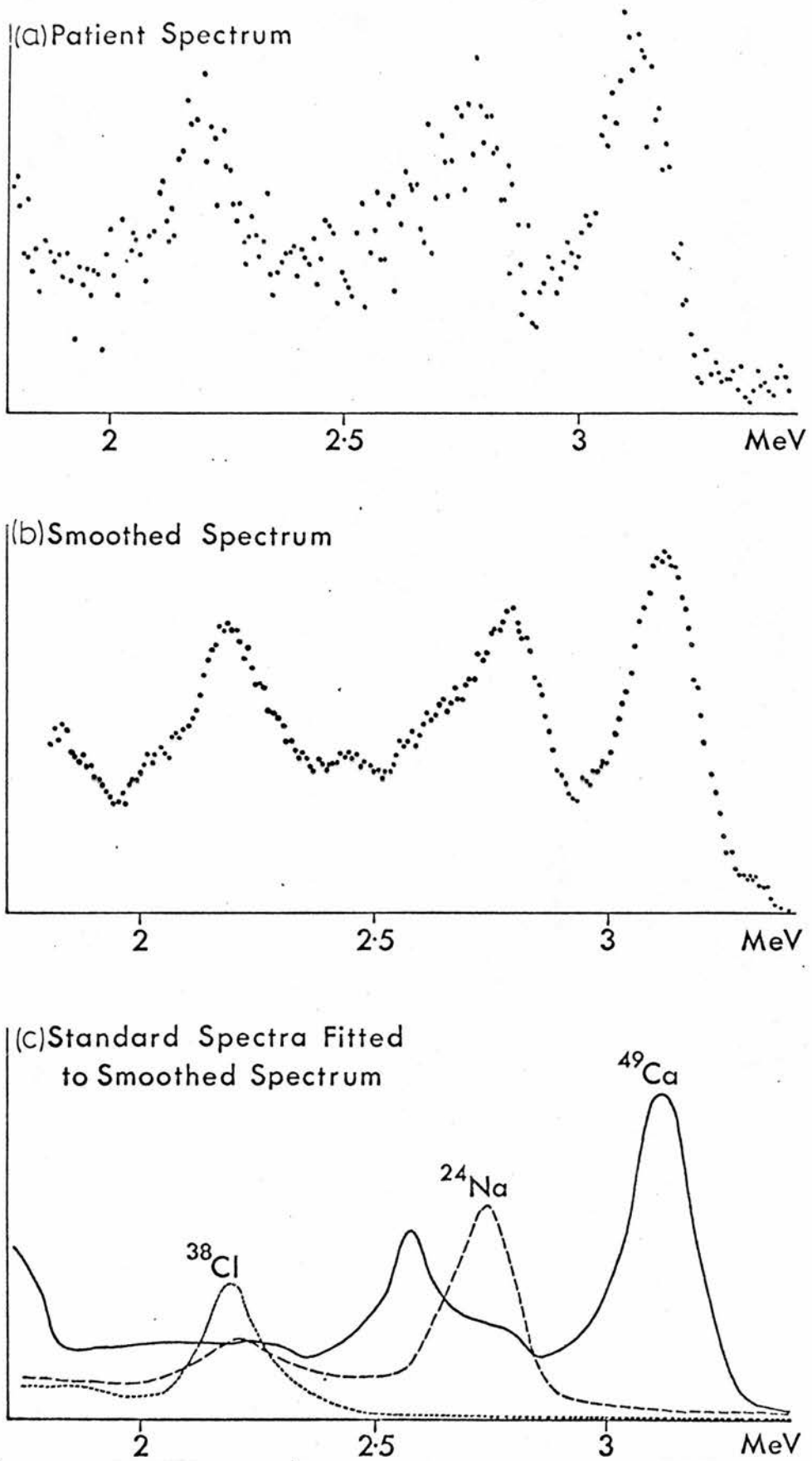
The effect of summing the 1.60 MeV peak of ^{38}Cl and the 1.37 MeV peak of ^{24}Na was investigated. Analysis of a spectrum from a cadaver limb showed that these were the

only peaks whose summing could produce an error in the calcium region. Three perspex tubes 20 cm long and internal diameter 1.2 cm were filled with either NaOH, CaCl_2 or H_2O . The two tubes containing the NaOH and CaCl_2 were irradiated so that the ratio of the activity of the ^{24}Na and ^{38}Cl was similar to that of the cadaver limb. The tubes were measured together in the part-body counter and then separately with the water tube, and the spectra were measured from 2.9 to 3.1 MeV. No evidence was found of any significant contribution to the background from the summing of the two peaks at 2.97 MeV.

The main interference to the calcium counts was from neighbouring peaks, in particular, ^{24}Na . Now the peaks of ^{24}Na and ^{49}Ca at high energies were not simple photo-peaks but both had a lower secondary peak at 0.511 MeV below the photopeaks (Fig. 4.1). These peaks were due to the escape from the crystal of one of the products of pair production which occurred at high energies. Close examination of the calcium standard spectrum revealed an extremely small peak at 1.02 MeV below the photopeak due to the escape of both pair production products. The presence of this secondary peak meant that it was not possible simply to integrate over the sodium photopeak and then calculate the percentage contribution in the calcium region.

The technique that had been frequently used to calculate the sodium contribution, particularly in whole body measurements, was to allow the ^{49}Ca to decay then

Figure 4.1



measure the contribution of the two longer lived isotopes. This technique however was not suitable in partial body sites because of the recirculation of particularly ^{24}Na in the soft tissue. It has been shown (Spinks et al 1976a) that the clearance half time for sodium in the hand can be as short as 26 min, thus any value of the sodium contribution could be grossly underestimated.

Two methods were used to calculate the calcium contribution by comparing the complex spectrum with standard spectra from the separate elements which were irradiated and counted in the same geometry. Both methods have their advantages and were used on all patient data to obtain a direct comparison.

4.2 Simultaneous Equations Method

This method enabled a quick and fairly accurate determination to be made of the calcium contribution in the patient spectrum without the use of a computer. It was assumed that the contribution from ^{38}Cl was negligible and so the following integrations were performed on the complex spectrum and the two standard spectra. The standard spectra were obtained by irradiating and counting bone-like phantoms in the same geometry as used for the patient spectrum. The standards were long perspex tubes of internal diameter 3 cm, containing NaOH or pure calcium metal.

Let P_{Ca}	=	counts in complex spectrum in region	2.94/3.30	MeV
P_{Na}	=	" " " " " "	2.60/2.94	
C_{Ca}	=	" " calcium standard " "	2.94/3.30	
C_{Na}	=	" " " " " "	2.60/2.94	
S_{Ca}	=	" " sodium standard " "	2.94/3.30	
S_{Na}	=	" " " " " "	2.60/2.94	

So if x = scaling factor for calcium Std
and y = " " " sodium "

$$\therefore P_{Ca} = xC_{Ca} + yS_{Ca}$$

$$P_{Na} = xC_{Na} + yS_{Na}$$

Hence the values x and y were easily calculated and the calcium contribution in the 2.9/3.3 MeV range was determined. The activity measured in the standard spectra was such that C_{Na} and S_{Ca} were each greater than 10^4 Counts, so statistical errors in the standards were minimal.

4.3 Spectral Stripping Method

This technique was considerably more complicated than the previous one in that it required the use of a computer if it were to be used routinely for large numbers of patient measurements. It basically involved fitting the three standard spectra simultaneously using a least squares technique to the complex spectrum. The following matrix algebra was used.

Let n = no. of points in spectrum

P_i = counts in i th channel of patient spectrum

S_{ki} = counts in i th channel of k th standard spectrum

Z_k = scaling factor of the k th standard

W_i = weighting factor of each point

The least squares value must be minimised.

$$\therefore \text{Minimise } x^2 = \frac{1}{n-1} \left[\sum_{i=1}^{i=n} W_i \left(P_i - \sum_{k=1}^{k=3} Z_k S_{ki} \right)^2 \right]$$

$$\text{so } \frac{d(x^2)}{dZ_k} = 0$$

$$\therefore \sum_{j=1}^{j=3} Z_j \sum_{i=1}^{i=n} W_i S_{ki} S_{ji} = \sum_{i=1}^n W_i S_{ki} P_i \quad (k = 1, 2, 3)$$

Expressed in matrix form:

$$SWS^T Z = SWP$$

$$\therefore Z = (SWS^T)^{-1} SWP$$

where

Z = a 3×1 column matrix of unknown scaling factors

S = a 3×200 matrix. 200 spectrum points are used

S^T = a 200×3 transpose matrix of S

W = a 200×200 diagonal matrix with $W_{ij} = 0$ for
all $i \neq j$

P = a 200×1 column matrix of the complex spectrum

A computer programme was written in Fortran IV to compute the value of Z_k . Initially the programme was written for a Rad 8 computer with 16K core memory but it has subsequently been transferred to a Varian V72 machine. In addition to fitting the three standard spectra to the complex spectrum, it was possible to correct for any drift that had occurred in the electronics (Section 3.2).

The patient spectrum and the sodium and calcium standard spectra, in the energy range 1.8 MeV to 3.4 MeV, were stored on paper tape which was fed into the computer. The calcium and sodium standard (Section 5.5) were measured each day to check the apparatus and the relevant day's standards were always fed in with the patient tape. A single ^{38}Cl standard was stored in the computer and used for all the calculations.

Once the data had been fed into the computer, the patient spectrum was smoothed by fitting a polynomial (Quittner 1972). This method was chosen in preference to a weighted mean technique because it was less likely to distort the peaks and valleys of the spectrum. The F.W.H.M. of the calcium peak was about 16 channels so a 13 point polynomial of the second degree was fitted to the spectrum (Fig. 4.1(b)).

After smoothing the patient spectrum, the product SW was computed. The weighting matrix was a combination of two separate weighting factors so that:

$$W_i = \alpha_i \times f(P_i)$$

where $\alpha_i = 1$ for $1 \leq i \leq 89$ 1.80 MeV to 2.50 MeV
 $= 3$ for $90 \leq i \leq 139$ 2.50 MeV to 2.90 MeV
 $= 5$ for $140 \leq i \leq 200$ 2.90 MeV to 3.40 MeV

and $f(P_i) = \sqrt{P_i}$

It was thought necessary to include α_i to weight different portions of the spectra because the main peaks had progressively larger amounts of interference from other peaks as the energy decreased. The values of α_i were determined experimentally from eight repeated measurements of a cadaver limb. The values of 1, 3, 5 above were found to improve the standard deviation of the eight measurements from when a value $\alpha_i = 1$ for $i = 1, 200$ was used. As the standard deviation of each individual point in the complex spectrum approximated to $\sqrt{P_i}$, the second component of the weighting factor was thus chosen so that the weighting between points was proportional to their relative errors. The value of $f(P_i)$ was equal to the inverse of the statistical coefficient of variation of point P_i .

$$\text{i.e.} \quad f(P_i) = \left[\frac{\sqrt{P_i}}{P_i} \right]^{-1} = \sqrt{P_i}$$

The programme then computed the matrix SWS^T and inverted this 3×3 matrix using the Gauss-Jordan technique. Once the scaling factors Z_k had been obtained, the chi-squared value was calculated.

$$\chi^2 = \sum_{i=10}^{i=90} \left[\frac{\left(P_i - \sum_{k=1}^{k=3} Z_k S_{ki} \right)^2}{\sum_{k=1}^{k=3} Z_k S_{ki}} \right] \quad (\text{where } \chi^2 = \text{Chi}^2)$$

The standards were then shifted to correct for drift. This was done iteratively by moving the standards individually, in the order Cl, Na then Ca, and recalculating Z_k until the minimum χ^2 value was obtained. The standards fitted to a typical patient spectrum is shown in Figure 4.1(c). A block diagram of the program is shown in Figure 4.2 and a listing is given in Appendix III.

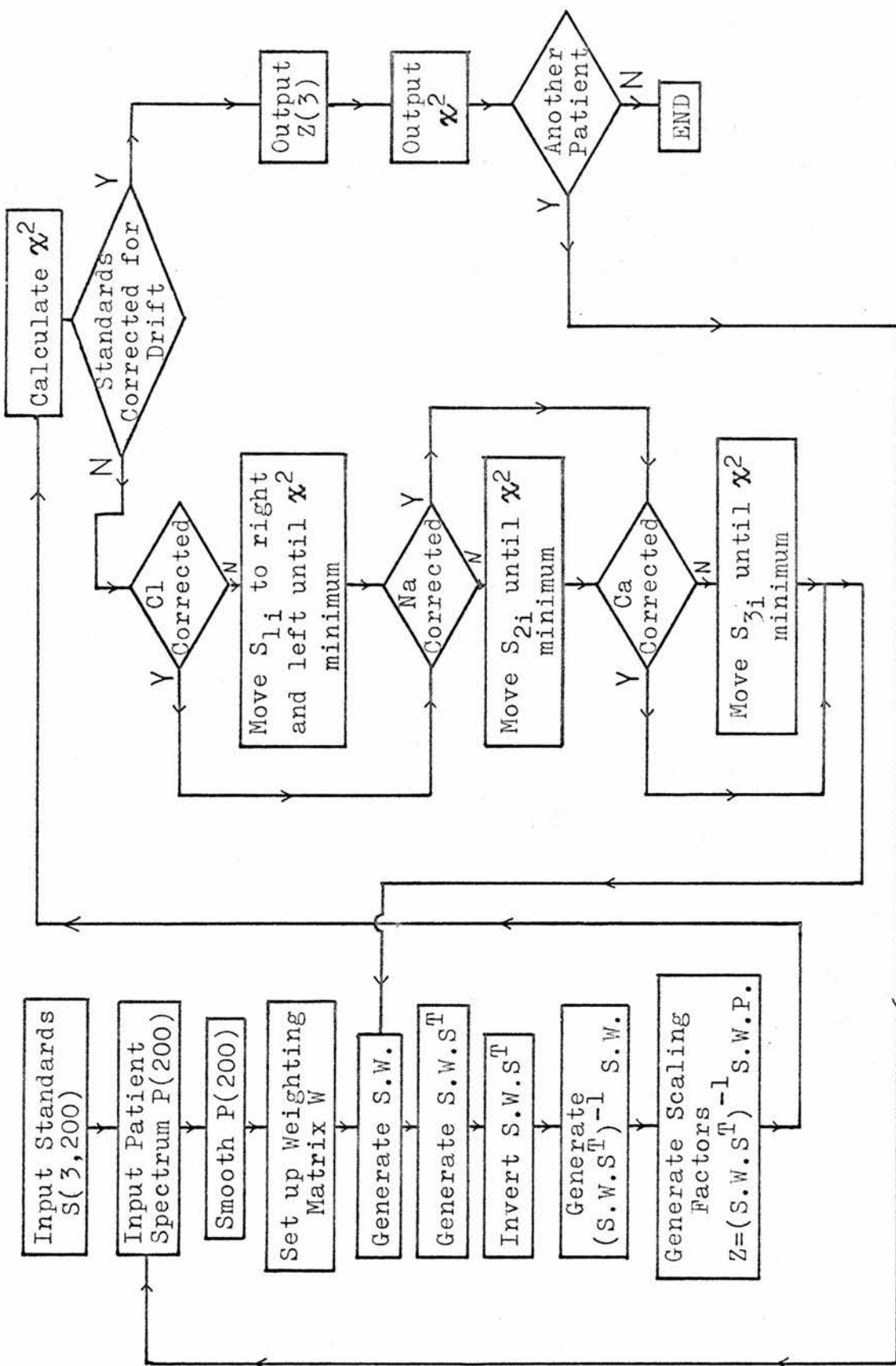
4.4 Comparison of the Methods of Spectral Analysis

The intrinsic accuracy of the two methods of spectral analysis was obtained by repeated measurements on a patient spectrum which was randomly altered within its theoretical statistical limits. A patient spectrum was chosen at random and each of the 200 points, $P(I)$, in the region 1.8 MeV to 3.4 MeV was randomly changed in a normal distribution with a mean at $P(I)$ and a standard deviation $\sqrt{P(I)}$.

Now normally distributed random numbers were obtained from uniformly distributed random numbers using the formula:

FIGURE 4.2

Block Diagram of the Spectral Stripping Program



$$Y = \frac{\sum_{i=1}^{i=K} x_i - \frac{K}{2}}{\sqrt{\frac{K}{12}}} \quad \text{---(1)}$$

where x_i were uniformly distributed random numbers $0 < x_i < 1$ (Hamming 1962). The value Y was sufficiently normally distributed with the value $K = 12$ which simplified the equation above:

$$Y = \sum_{i=1}^{i=12} x_i - 6.0 \quad \text{---(2)}$$

Normally distributed random numbers X^1 about a value X which had a standard deviation S were therefore:

$$X^1 = Y * S + X \quad \text{---(3)}$$

The single patient spectrum $P(I)$ was altered using an array of 200 normally distributed random numbers, $RAND(I)$, using equation (2). The values of $RAND(I)$ were obtained using the uniform random number generator which was available in a PDP 11 computer. The values of $RAND(I)$ were tested for normality using equation (3) with values $X = 10,000$ and $S = 100$, and a histogram was plotted. The resultant mean and standard deviation of all the values was 10,000.63 and 97.81 respectively, 69% of all the 200 values being within 1 S.D. of the mean, and the histogram gave every appearance of being a normal distribution. The patient spectrum was therefore altered and

became:

For $I = 1,200$

$$P(I) = P(I) + \text{RAND}(I) \times (P(I))^{\frac{1}{2}}$$

The patient spectrum was altered in this way and processed using both the simultaneous equations and matrix method of spectral analysis. This was repeated 12 times starting at different places in the array $\text{RAND}(I)$, and the results are shown in Table 4.1.

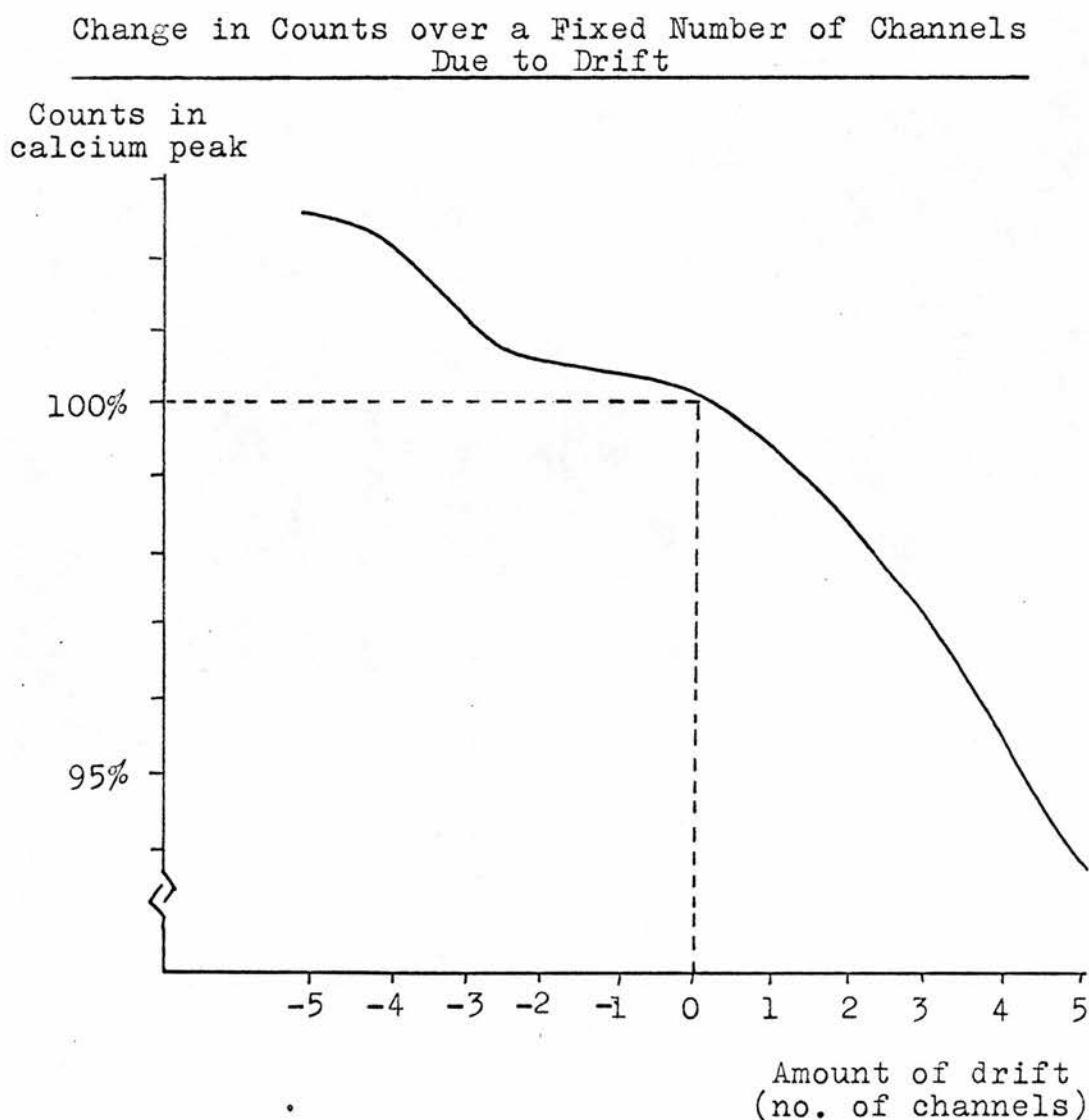
<u>TABLE 4.1</u>				
Matrix Method			Simultaneous Equations Method	
	Na scaling factor	Ca counts 2.9/3.3 MeV	Na scaling factor	Ca counts 2.9/3.3 MeV
Mean	.0059969	4535.7	.0065815	4655.9
S.D.	.00030858	96.9	.00039446	109.9
C.V.	5.15%	2.14%	5.99%	2.36%

It can be seen that the matrix method of analysis gave a lower coefficient of variation for both sodium and calcium. The 2.6% higher calcium count and the 9.8% higher sodium contribution obtained using the simultaneous equation method was due to the absence in the calculation of the contribution from ^{38}Cl .

An additional error that could be present in the simultaneous equations method was that of drift in the

electronics (Section 3.2). The integration of the patient spectrum was performed between fixed channel intervals on the M.C.A. so if any drift had occurred in the time between the patient measurement and the standard measurements an error would be introduced. Poor statistics in the unsmoothed patient spectrum on the multichannel analyser made it impossible to judge a drift of up to 3 channels ($\equiv 24$ KeV) in either direction. The possible error due to drift is shown in Figure 4.3.

FIGURE 4.3



The matrix stripping technique, with its greater intrinsic accuracy, and its ability to correct for drift, appeared to be superior. With a fast paper tape reader, the data could be fed quickly into the computer and so analysis took only a matter of minutes for each patient. However a fairly large computer was required to process the data in a reasonable time, whereas the simultaneous equation method could be used with very modest facilities. In the following chapter, both methods are compared using a large number of patient results to determine whether the sophistication of the matrix method was warranted.

CHAPTER 5.

CHAPTER 5

REPRODUCIBILITY AND IRRADIATION PROGRAMME

The two topics of firstly reproducibility, the precision of the method, and secondly the irradiation programme, when and how patients are to be measured, are discussed together in this chapter because of their interdependence. It will be seen how initial phantom measurements of the reproducibility determined the irradiation programme, and how this in turn led to a much more accurate estimation of the reproducibility.

5.1 Cadaver Reproducibility

Using the first irradiation geometry, eight repeated measurements were performed on a cadaver limb. These measurements were performed over a period of 24 days so that sufficient time elapsed between measurements to let the ^{24}Na decay. The timing was the same for all eight measurements; 10 min irradiation, 2 min delay and 1000 s count.

Perspex tubes of Na and Ca were also irradiated to obtain standard spectra and the calcium counts from the cadaver limb were calculated using the method of simultaneous equations. The standard deviation of these values was taken as the reproducibility and was found to be 3.33% (coefficient of variation) of which 2.23% was due to counting statistics.

From the figure for the reproducibility of the method, it was possible to state the percentage change that could be measured in a patient over a period of time with any degree of significance. The calculation of the "least significant change", however, varied considerably from one centre to another where sequential patient measurements were being performed. In view of the importance of this figure for interpreting individual patient results, this situation gives cause for concern.

The Washington group (Nelp et al 1972b) stated that changes of ± 1 S.D. were measurable, as did the Aberdeen group (Catto et al 1973b). Also in clinical studies at Brookhaven (Cohn et al 1971), changes of greater than 1 S.D. were said to be significant. In Birmingham however (Hosking et al 1972a), the reproducibility was quoted as 1.7% and the least significant change as 4% which was 2.35 S.D.

One problem was deciding on the degree of significance when calculating the least significant change from the reproducibility figure. In the following analysis of the least significant change, the level of significance was taken as $p < 0.05$, which was thought to be necessary for patient studies.

5.2 Least Significant Change

The standard deviation (reproducibility) of the cadaver measurements, S , was an estimate based on 8 values, of the true standard deviation σ . Consider two measure-

separated by a time interval to be x_1 and x_2

$$\therefore \frac{x_1 - x_2}{\sqrt{s_1^2 + s_2^2}} \sim t_{m-1}$$

The change is significant iff:

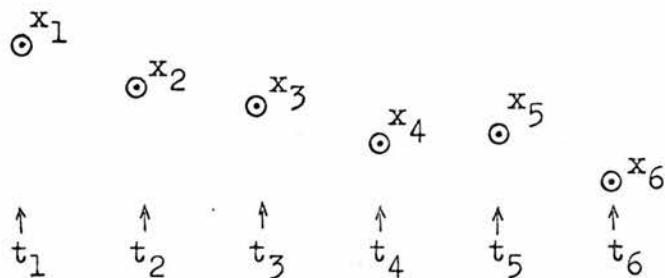
$$\begin{aligned} |x_1 - x_2| &\geq \sqrt{2} \times S \times t_{m-1} & (S_1 \simeq S_2) \\ &\geq \sqrt{2} \times 3.33\% \times 2.37 \end{aligned}$$

$$\text{Least significant change} = \underline{11.16\%} \quad (p < 0.05)$$

This value was too high for patient studies to be feasible in the short term. The irradiation time for the cadaver measurements was 10 min so little would be gained by increasing the irradiation time; the reduction in the statistical contribution of the reproducibility would be minimal compared to the increased dose.

Permission was obtained from the M.R.C. for an annual dose equivalent to 6 measurements, so a decision had to be made when these were to be performed to measure a change over a 6 month period. The least significant change was calculated in the three following situations.

(i) Six measurements $x_1 \dots x_6$ at monthly intervals $t_1 \dots t_6$

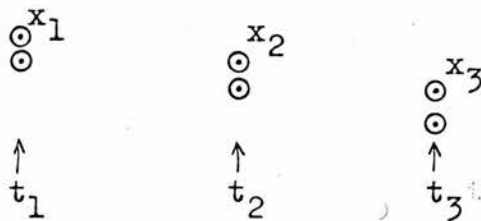


$$b = \text{slope/month} = \frac{\sum (x_i - \bar{x})(t_i - \bar{t})}{\sum (t_i - \bar{t})^2}$$

$$\text{S.E.}(b) = \frac{S}{(\sum (t_i - \bar{t})^2)^{\frac{1}{2}}}$$

$$\begin{aligned} \therefore \text{Least significant change} &= \frac{10}{\sqrt{70}} \times S \times t_{m-1} \\ &= \underline{9.43\%} \quad (p < 0.05) \end{aligned}$$

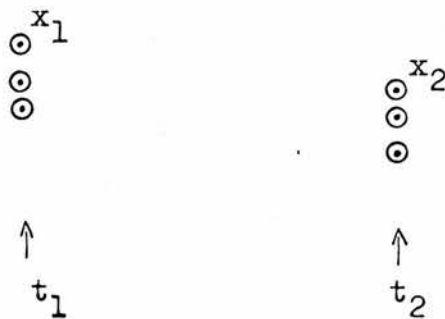
(ii) Three sets of two measurements x_1, x_2, x_3 at times t_1, t_2, t_3



$$\text{Standard error of each set of two} = \frac{S}{\sqrt{2}}$$

$$\text{Least significant change} = \underline{7.89\%} \quad (p < 0.05)$$

(iii) Two sets of three measurements x_1, x_2 at times t_1, t_2



$$\text{Least significant change} = \underline{6.44\%} \quad (p < 0.05)$$

5.3 Irradiation Programme

In the previous section it is seen that two sets of three irradiations give the lowest value of the least significant change. In the first sets of patient studies, changes were expected over a six-month period, so the two sets of three measurements were adopted as the most suitable irradiation programme.

One additional advantage of repeated sets of three measurements on patients was that a much more accurate reproducibility figure could be obtained. By combining the standard deviations of all the sets of three measurements, a figure for the reproducibility was achieved which included patient movement, a factor which was ignored when phantom or cadaver measurements were performed. In addition the final value of S obtained would be based on a very large number of results so the figure for t_{m-1} would tend to 1.98.

It was also felt that no extra information would be gained by six separate measurements because changes over this period were likely to be so small that it would be impossible to follow the trend of any gain or loss.

5.4 Patient Reproducibility

Using the sets of three measurements from the patients, reproducibility figures were obtained for both irradiation geometries using both data processing techniques. From each set of three readings the mean and the standard

deviation were calculated, the latter being divided into two components C.V._S and C.V._M where:

C.V._S = statistical coefficient of variation

C.V._M = coefficient of variation due to other variables such as movement etc.

These were calculated from \overline{Ca} , the mean calcium counts in the range 2.9/3.3 MeV and C.V._T the total coefficient of variation.

$$C.V._S = \frac{\sqrt{\overline{Ca} + bgd}}{\overline{Ca}}$$

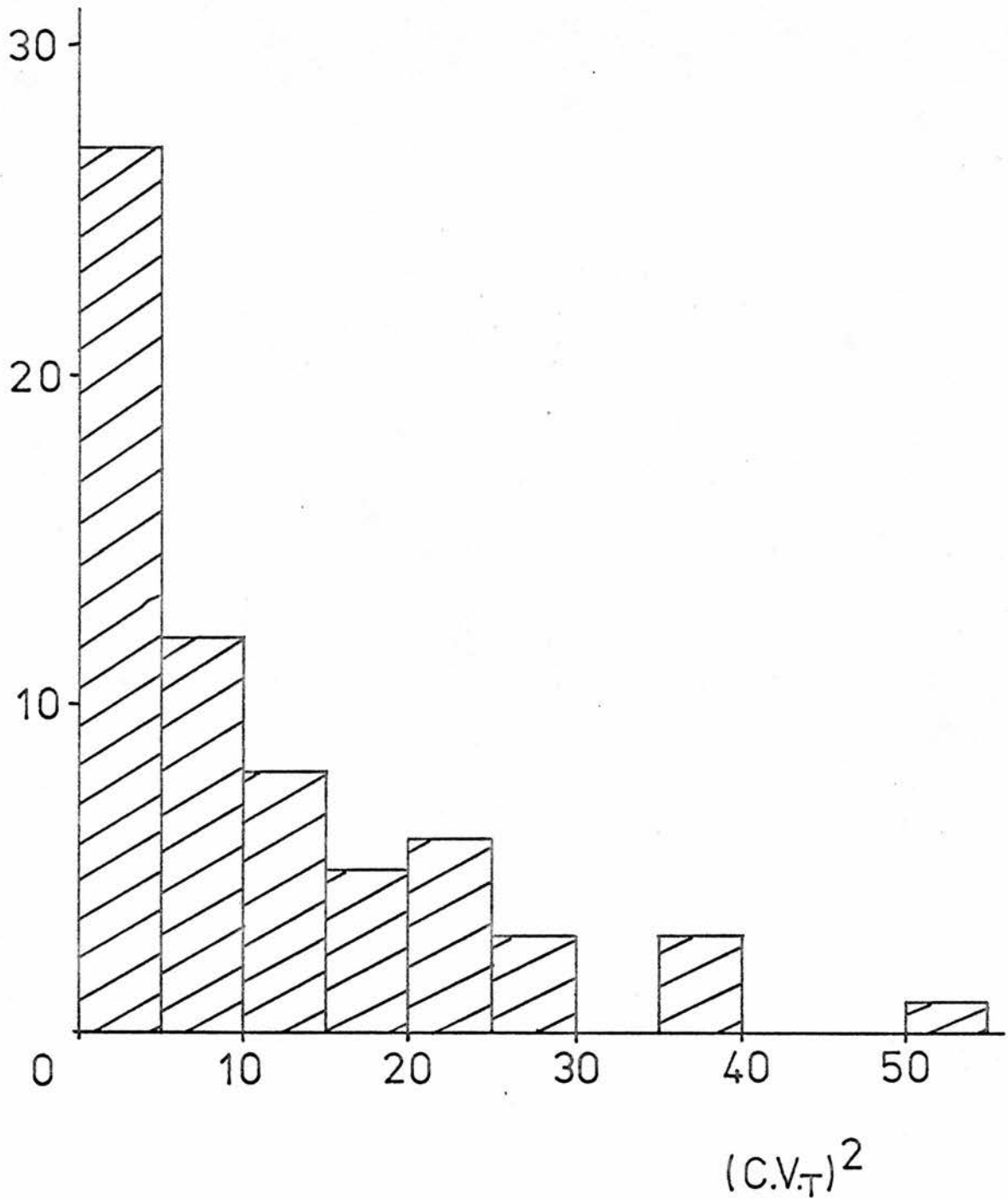
$$C.V._M = \sqrt{(C.V._T)^2 - (C.V._S)^2}$$

It was necessary to separate the two components in this way because of the large variation in \overline{Ca} from patient to patient and hence the large variation in C.V._S. The component C.V._M should be independent of \overline{Ca} and so was calculated separately. All the values from the different patients were combined to give a C.V._M for the different irradiation geometries and processing techniques.

A histogram of $(C.V._T)^2$, a function of the variance, of 64 sets of three patient measurements is shown in Figure 5.1. It is seen that the distribution is exponential, as would be expected from a homogenous distribution of sets of three measurements. If the number of measurements in each set were to increase, so the histogram would tend to a symmetrical normal distribution. The results of

Figure 5.1

Histogram of $(C.V._T)^2$ of 64 sets
of triple patient measurements



analysis of patient data is shown in Table 5.1. Included in the table is a figure for the mean total coefficient of variation ($\overline{C.V._T}$) and the least significant change (L.S.C.) based on a calcium count of 2025 and 3501 for irradiation geometries (A) and (B) respectively. These values of the calcium counts are the means of all the calcium counts for each geometry with the initial sources.

TABLE 5.1						
	Matrix Method			Simultaneous Equations		
Geometry	C.V. _M	C.V. _T	L.S.C. p<0.05	C.V. _M	C.V. _T	L.S.C. p<0.05
(A)	2.20	3.14	5.13%	2.66	3.45	5.63%
(B)	1.93	2.57	4.20%	2.04	2.65	4.33%

where the number of sets of three measurements that these results are based on were 75 and 68 for irradiation geometries (A) and (B) respectively.

The L.S.C. was calculated assuming two sets of three measurements will be made. It is seen that irradiation geometry (B) was superior, as was expected, and that the matrix method of calcium analysis was marginally better than the simultaneous equations method. The precision (standard error) of the mean of each set of three measurements for geometries (A) and (B), using the matrix method, was 1.81% and 1.48% respectively. It was felt that

$p < 0.05$ was the necessary level to determine significance in the individual patient and so the relevant value was used to determine the least significant change.

5.5 Apparatus Stability

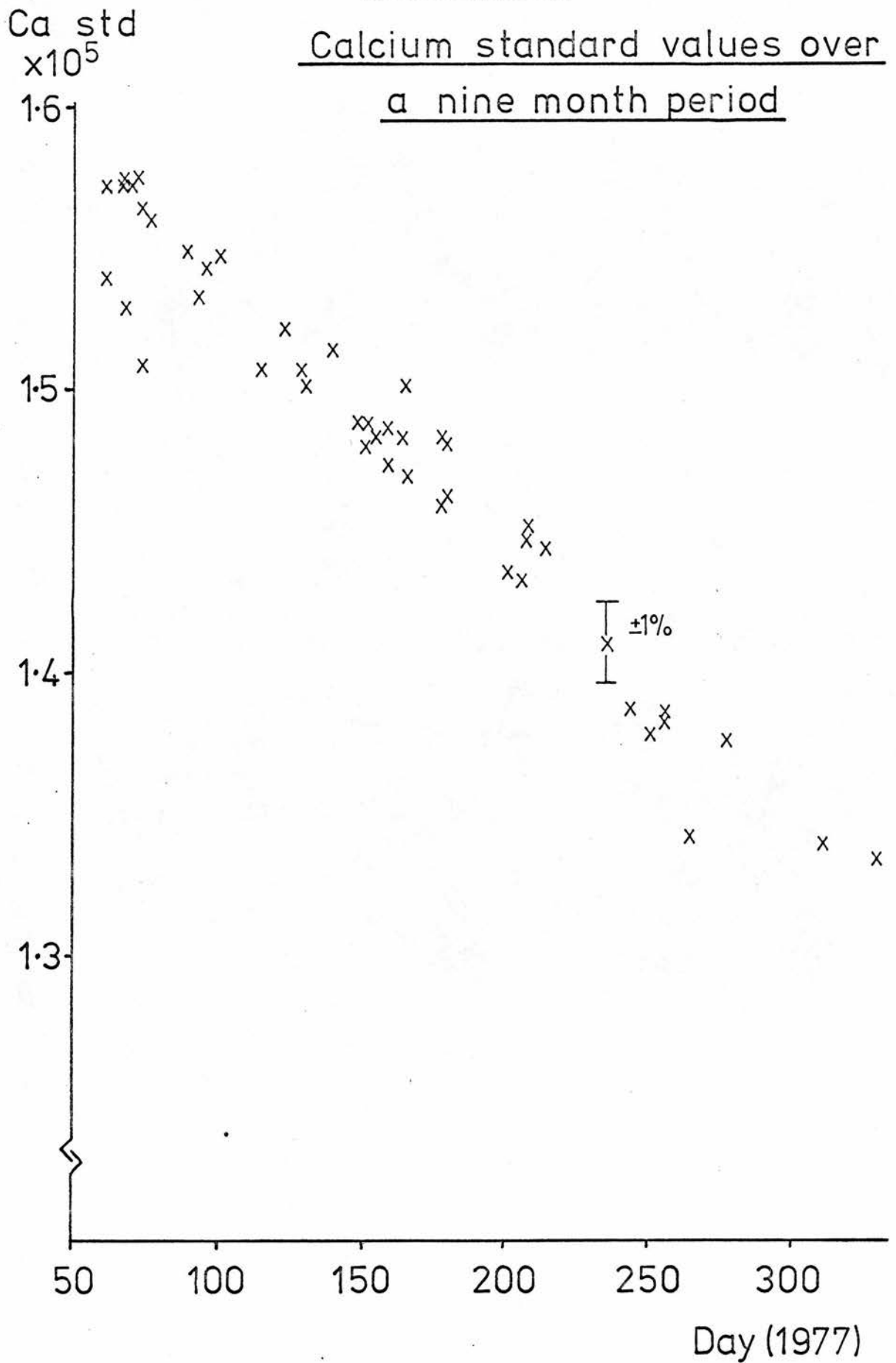
The long term stability of the apparatus was demonstrated from the calcium standard measurements that were performed on each day that a patient was measured. Figure 5.2 shows the standard measurements with the water bath and the new sources over a nine-month period.

The occasional low standard value was due to the end of one of the source delivery tubes not being pushed fully into the wax reflector. The frequent changing of the irradiation apparatus, or the use of the chamber for experimental purposes, made such occasional mistakes inevitable.

A more serious problem was discovered in the irradiation apparatus from the standard results (not shown in Figure 5.2). When the water bath was first used for patient measurements, it was discovered that, over the first month, the gradual decrease in counts from the standard was greater than could be accounted for by the decay of the ^{252}Cf sources. Examination of the apparatus showed that warm water in the water bath had caused the sides to bulge slowly, thus gradually increasing the source separation. The water bath was subsequently strengthened and the standard values used to correct the patient values.

Figure 5.2

Calcium standard values over
a nine month period



CHAPTER 6.

CHAPTER 6

PATIENT PROCEDURES

Details have been given in the preceding chapters concerning the basic method for clinical neutron activation measurements. In this chapter details will be given of the procedure adopted for patient measurements, both with respect to activation analysis and to other existing methods of measuring the calcium status of a patient, with which comparisons will be made.

6.1 Activation Analysis

The initial contact with a prospective patient was made by one of the medical staff associated with the project. The purpose of the particular study was explained from the medical point of view and once the patient's consent had been obtained, the physicist explained exactly the practicalities that were involved for the patient. Once the patient's consent had been obtained, the only criterion for his removal from the study was at his own request.

At the start of the patient's first visit for activation analysis he was shown how to sit and position himself in the partial body counters. This was essential to reduce the delay time between activation and detection. The height of the chair was adjusted and positioned so that his forearm was horizontal and his shoulder in line

with the arm rest.

The patient was moved into the irradiation chamber which was about 25 m distance and positioned in the irradiation apparatus. When irradiation geometry A was used the patient was positioned with his arm horizontal and with the hand grip at the centre of his clenched first (Fig. 6.1a). The separation and the position of the reflector/premoderator assemblies were checked and the top wax block placed in position. With irradiation geometry B the patient was positioned with his arm at an angle of 45° in the water bath which had previously been warmed to a comfortable temperature (Fig. 6.1b). The patient's arm was strapped into place making sure that his forearm was resting on the arm rest along its entire length and then the level of the water was adjusted so that it was level with the overflow.

After warning the patient that the sources were likely to arrive into position with a loud "click" and reminding them not to dawdle between the end of the irradiation and the start of the counting, the operator withdrew from the activation chamber and delivered the sources to the irradiation position. Once in position another burst of air was sent along the delivery tubes to ensure that the sources were in the correct position at the end of the tubes. Although this was done on every occasion it was only very rarely that the sources bounced back off the end stop when delivered into position the first time. The patients were irradiated for 10 min before March 1977 using the lower activity sources and for 4 min on later

FIGURE 6.1a



Irradiation geometry A with upper wax reflector block removed.

FIGURE 6.1b



Irradiation geometry B.

dates, a stopwatch being used for all the timing.

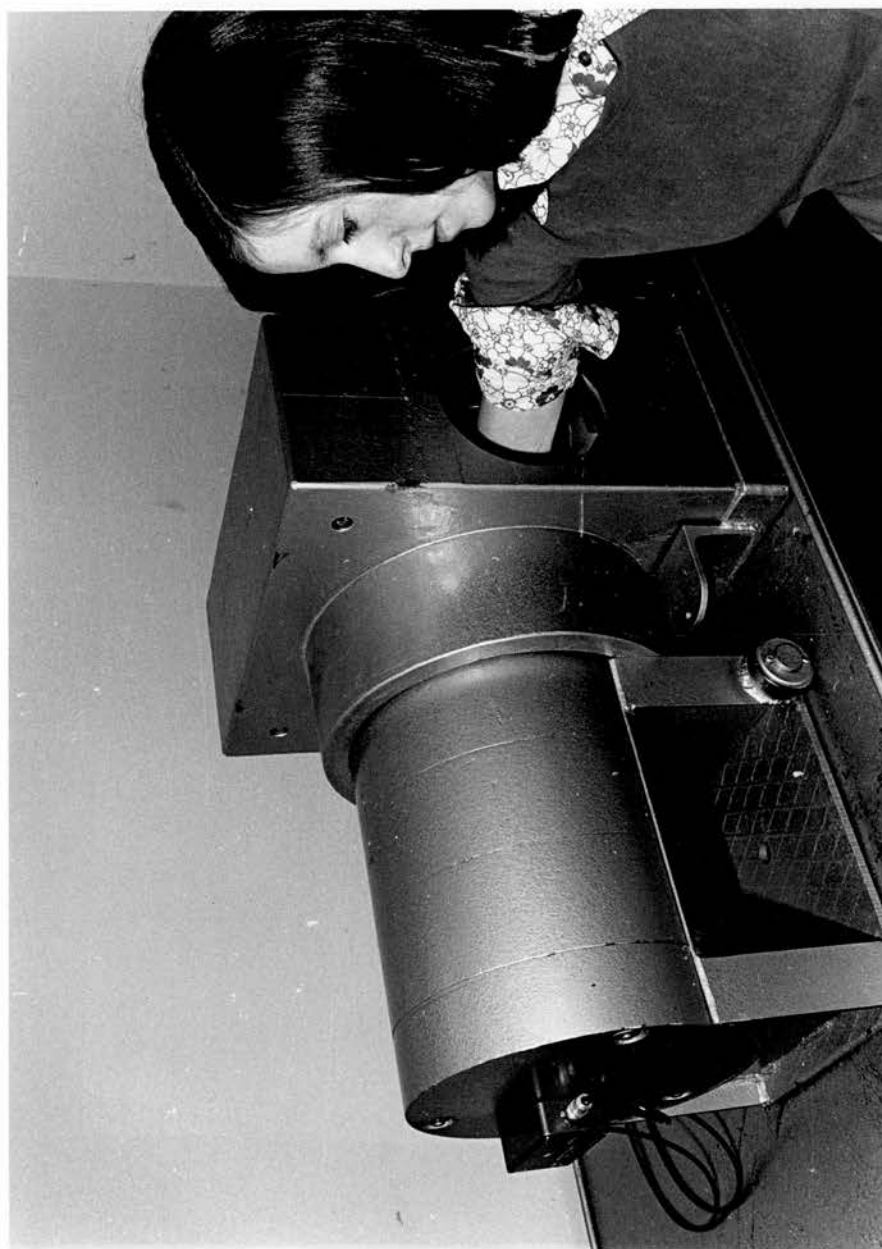
At the end of the irradiation the patient was moved into position in the part body counter generally with a delay of 1 min (Fig. 6.2). All the times were recorded so that the data of the patients whose delays were longer than 1 min could be corrected. The induced activity was measured for 1000 s, the timing being done automatically on the multi-channel analyser, though it was regularly checked with the stopwatch.

The three repeated measurements were performed at weekly intervals on the first group of patients studied, so each visit lasted about half an hour. This, unfortunately, was not possible with some of the later patient groups because the patients were unwilling to make repeated visits to the hospital. Hence the three measurements were repeated at hourly intervals after which time any activated calcium had nearly all decayed. The exact time interval between activations was noted to correct for any residual calcium. The activated ^{24}Na rose during the three measurements but in general the gross counts in the ^{24}Na region after the third measurement were approximately twice that after the first.

Before starting the patient trials some measurements were performed on patients' tibiae. The irradiation geometry was in principle the same as geometry A and photographs of irradiation and detection of tibia are shown in Figure 6.3.

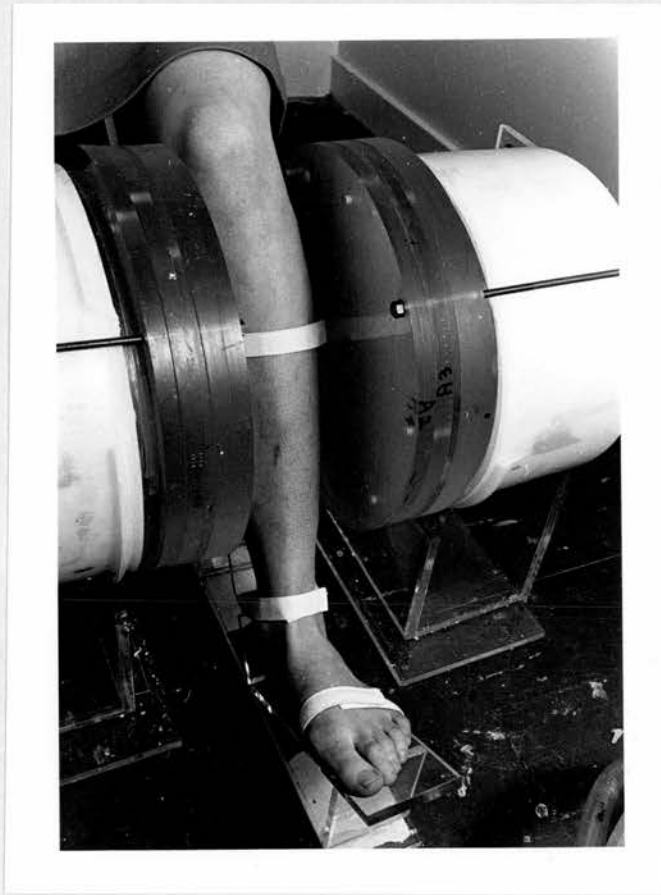
On each day that patient measurements were to be performed the E.H.T. supplies and the amplifier gain were

FIGURE 6.2

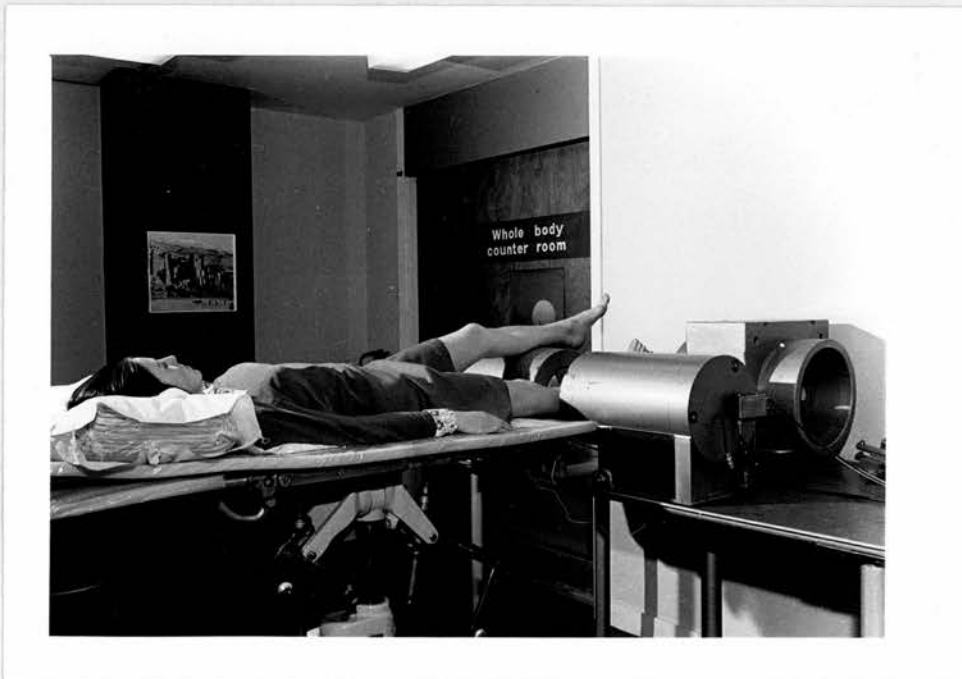


Partial body counter measuring a forearm with the centre shield.

FIGURE 6.3



Irradiation and detection of a patient's tibia.



calibrated using ^{24}Na and ^{60}Co first thing in the morning. The background was then measured with a wax arm phantom in the counter for 1000 s and stored in the second 512 channels of the analyser. The calcium standard was activated at mid-day for 30 min and counted for 1000 s following a one minute delay, care being taken to position the standard in the same place each time. Also at mid-day the sodium standard was measured, though it was not irradiated or counted for a specific length of time, but just long enough so that there were at least 10^4 counts in the region of the calcium photopeak.

6.2 Photon Densitometry

The technique of measuring the mineral density of bone by photon absorption has been well documented (Cameron and Sorenson 1967). The apparatus used for patient measurements was not one of the commercially available machines but was constructed in the department and used a source of 45 mCi of ^{241}Am instead of the more suitable ^{125}I for financial reasons.

The measurements were performed on the forearm at a distance 5 cm from the distal end of the radius. This was not the most uniform section of the bone but was likely to contain trabecular bone. The patient's arm rested in a water bath in such a position that his hand gripped a rod of perspex with his knuckles resting on the base of the water bath. The patient's humerus was held vertical with his elbow resting on the base of the water

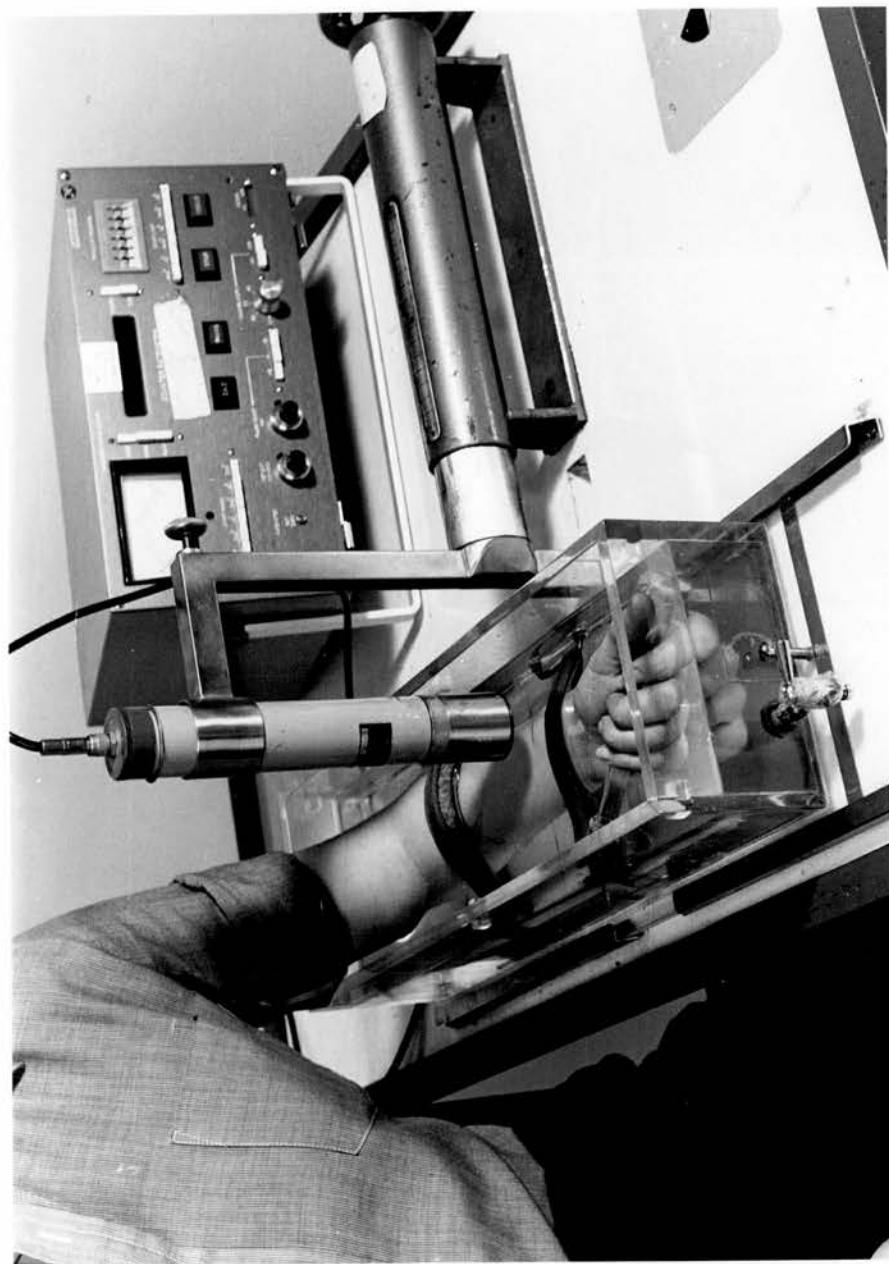
bath. In such a position the radius and ulna were held in a fixed position and did not overlap. The arm was strapped firmly in position using velcro straps and the bath was filled to cover the patient's arm (Fig. 6.4).

The detector was placed about 1 cm above the water level and the source and detector were scanned manually across the forearm. Attached to the detector was a 1.2 cm long and 0.5 cm wide collimator. Experiments scanning across a straight edge of aluminium gave a figure for the resolution, from 90% to 10% attenuation, of 0.26 cm. The aluminium was thick enough to give attenuation similar to a normal radius, and it was positioned 2 cm above the base of the bath. The maximum count rate obtained with a normal level of water was about $10,000 \text{ counts} \cdot \text{sec}^{-1}$.

With the patient's arm in position, the source and detector scanned across the radius in millimetre intervals, counting for 5 s at each position. At least 20 measurements were made before reaching the bone to enable the base line to be determined as accurately as possible, a precaution necessary when using ^{241}Am . Three complete traverses of the radius were made and all the data were collected on punch tape to be fed into the computer.

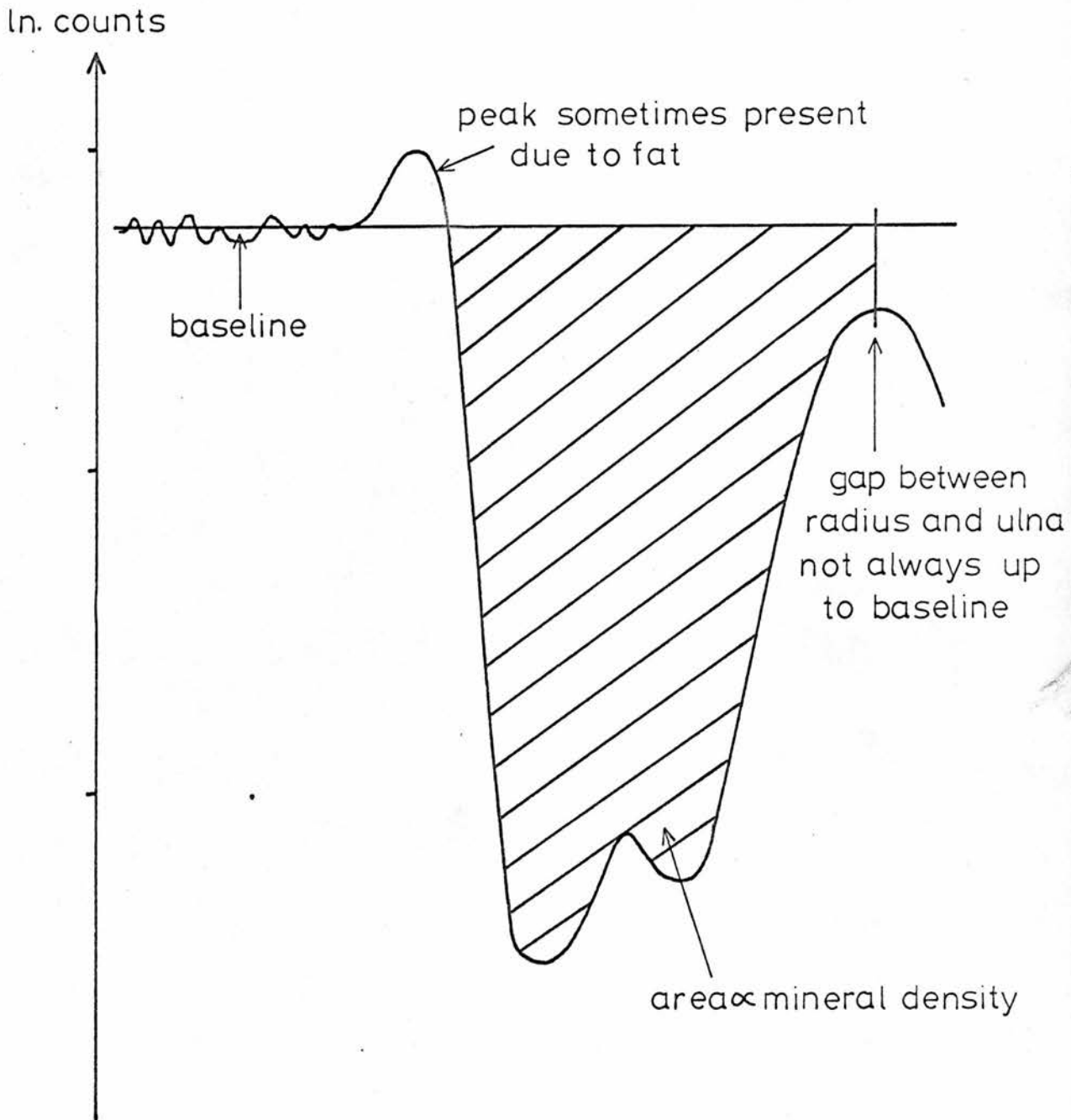
A result is shown in Figure 6.5 which illustrates all the possible problems involved in obtaining a figure of the mineral density. The major source of error is the baseline, as a change of 1% in the counts in the baseline will give an error of 2.0% in the mineral density. The precision of the value of the mineral density, based on 84 sets of three patient measurements, was 1.9%.

FIGURE 6.4



Patient's forearm in densitometry apparatus.

Figure 6.5
Scan across the radius illustrating
possible errors



6.3 Metacarpal Index

Radiographs can show changes in calcium content and there are several methods to quantify such changes. Radiographs of the hand have been particularly useful in the past to assess calcium changes in patients with renal osteodystrophy.

The patient's hand was placed as flat as possible on a low wooden box with the target of the X-ray tube 1.88 m above. Packets of non-screen film were used with the settings 75 KV and 250 mAs for 1 s. The film was then developed using an automatic processor. Ideally industrial film should be used and the developing done by hand to obtain the optimum contrast. This was not feasible and tests showed that the method used produced adequate radiographs.

Measurements were made using engineering vernier calipers on the second metacarpal (Fig. 6.6), and the values d , D and l could be measured to 0.01 cm. Many formulae have been used, combining the three variables together, to quantify changes in the cortex. It was decided to use the formula below for comparison with neutron activation analysis.

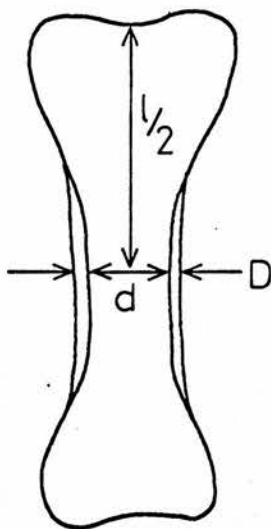
$$\text{Metacarpal Index} = D^2 - d^2$$

This was based on a recent review of quantitative radiogrammetry of cortical bone (Dequeker 1976), which stated that $D^2 - d^2$ is a slightly better index to use than the "combined cortical thickness" = $D - d$.

All radiographs were taken by the same radiographer and all measurements were performed by the same technician to reduce measurement errors.

FIGURE 6.6

Measurements on 2nd Metacarpal from Radiographs



CHAPTER 7.

CHAPTER 7

PATIENT STUDIES

7.1 Preliminary Patient Measurements

Before starting any clinical trials involving large numbers of patients it was decided to look at individual patients whose calcium level would be expected to change by a fairly large amount over a short time period. Apparatus similar to irradiation geometry A was used with just a single irradiation on each occasion, rather than the triple irradiation adopted for higher precision in the clinical trials. The purpose was simply to verify that neutron activation analysis could detect calcium changes in the patients.

Three patients were measured, two with Paget's disease of one peripheral bone but with the contralateral bone normal, and one patient suffering from hyperparathyroidism. The two patients with Paget's disease were treated with calcitonin and responded well to treatment. The third patient responded well to a parathyroidectomy.

Figure 7.1 shows the calcium level in patient C.R. during a 12 week treatment. The limb affected by Paget's disease had much more calcium than the normal tibia and there was a loss during treatment which is significant ($p < 0.05$) as would be expected. No change was detected in the normal limbs. The same result was found in the other patient (Fig. 7.2a) where no change was detected in the

Figure 7.1

Patient C.R.: Paget's disease in
left tibia

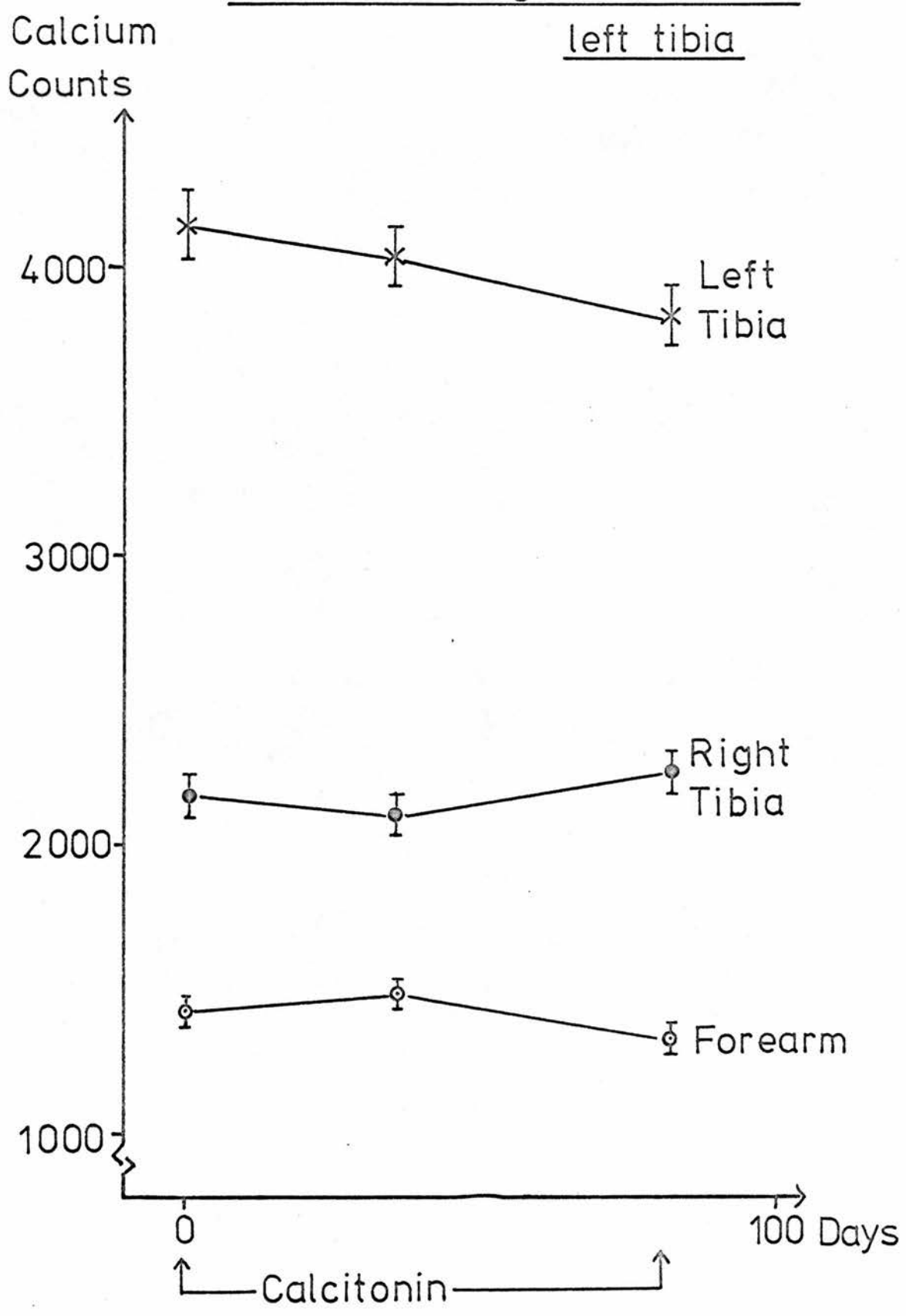
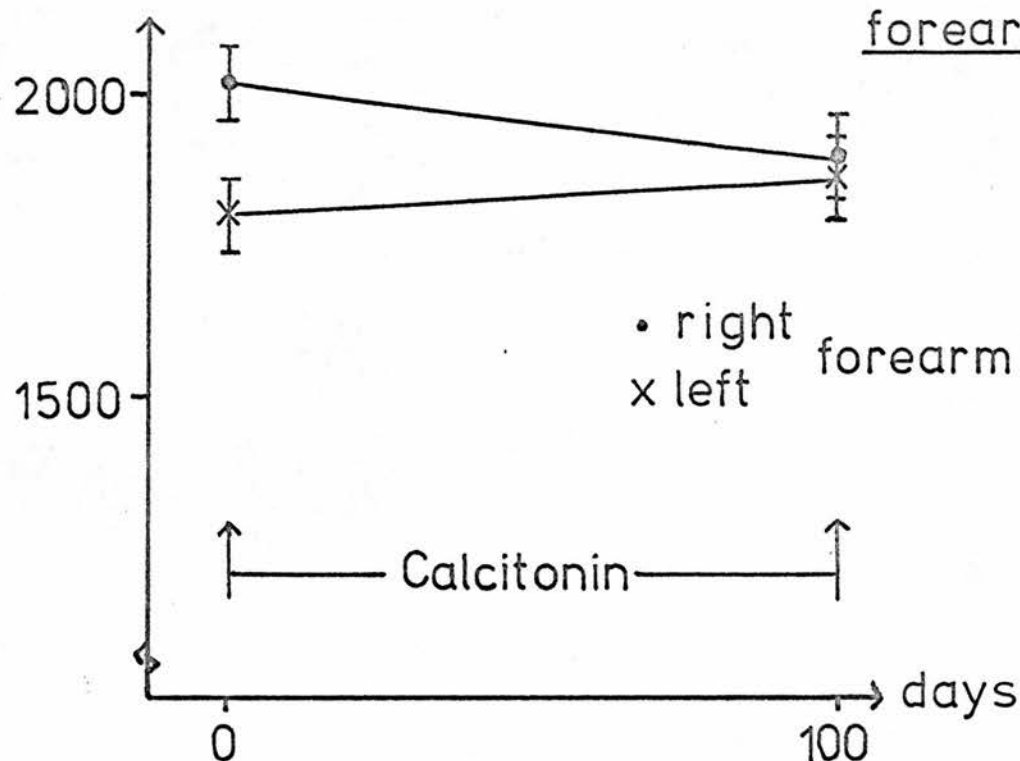
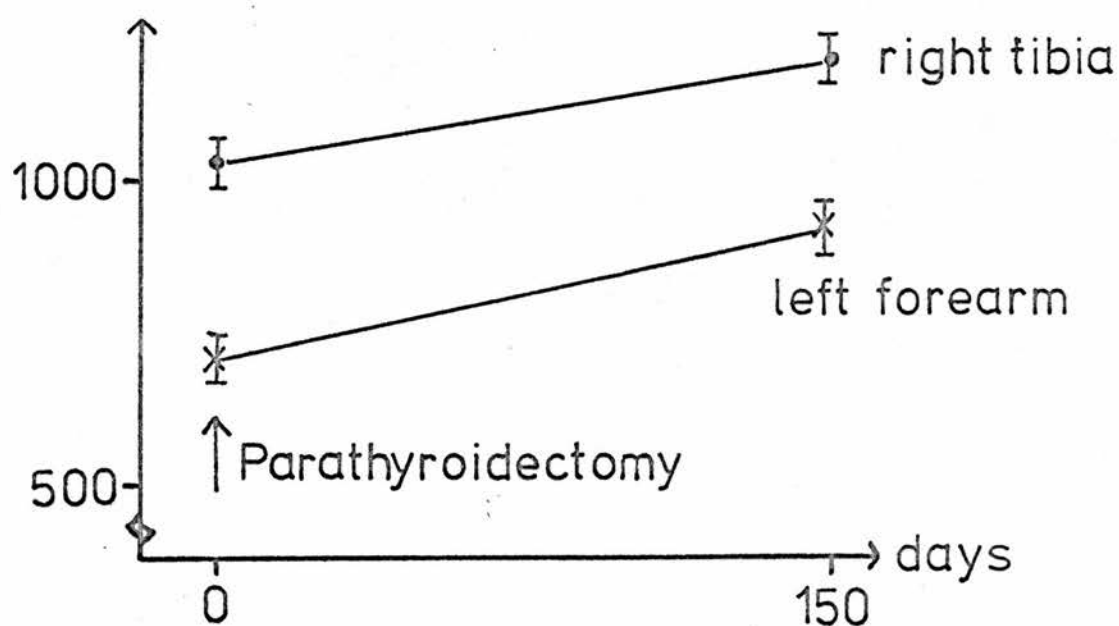


Figure 7.2

(a) Patient M.D.:Paget's disease in right forearm



(b) Patient M.F. Hyperparathyroidism



normal forearm but a possible significant loss in the diseased bone in response to treatment ($p < 0.10$).

In the patient with hyperparathyroidism (Fig. 7.2b), calcium in all the bone would be affected so both forearm and tibia were measured. As expected, calcium in both regions rose significantly over a period of 5 months post-operation ($p < 0.05$).

These initial patient studies showed that large calcium changes could be detected by neutron activation analysis. The following clinical trials would evaluate the technique in more extreme situations, i.e. where very small changes were expected or where the size of change, if any, was not known. It was for the purpose of these trials that the techniques described previously in this thesis were adopted.

7.2 1- α -Hydroxycholecalciferol and the Treatment of Renal Osteodystrophy

It is well known that patients with renal failure may develop metabolic bone disease and this has increasingly become a problem with the extended life expectancy due to the advances in haemodialysis. In many cases the treatment of this bone disease has become the major concern in the management of the patient.

The loss of calcium is probably due to the absence of a vitamin D metabolite, 1,25-dihydroxycholecalciferol (1,25-DHCC), which is produced in the kidney (Fraser and Kodicek 1970). Before vitamin D acts in the control of

calcium metabolism it is converted to a functional form in at least two metabolic steps. The first, 25-hydroxy-cholecalciferol (25-HCC), is synthesized in the liver from vitamin D and is the major form of circulating vitamin D. The second, more polar, metabolite, 1,25-DHCC, is three times more active and is derived from 25-HCC by hydroxylation in the kidney (Fig. 7.3).

A small number of patients with chronic renal failure have been given 1,25-DHCC for periods between two and six months (Henderson et al 1974). Healing of radiological rickets was observed but the difficulties in producing 1,25-DHCC have limited its value.

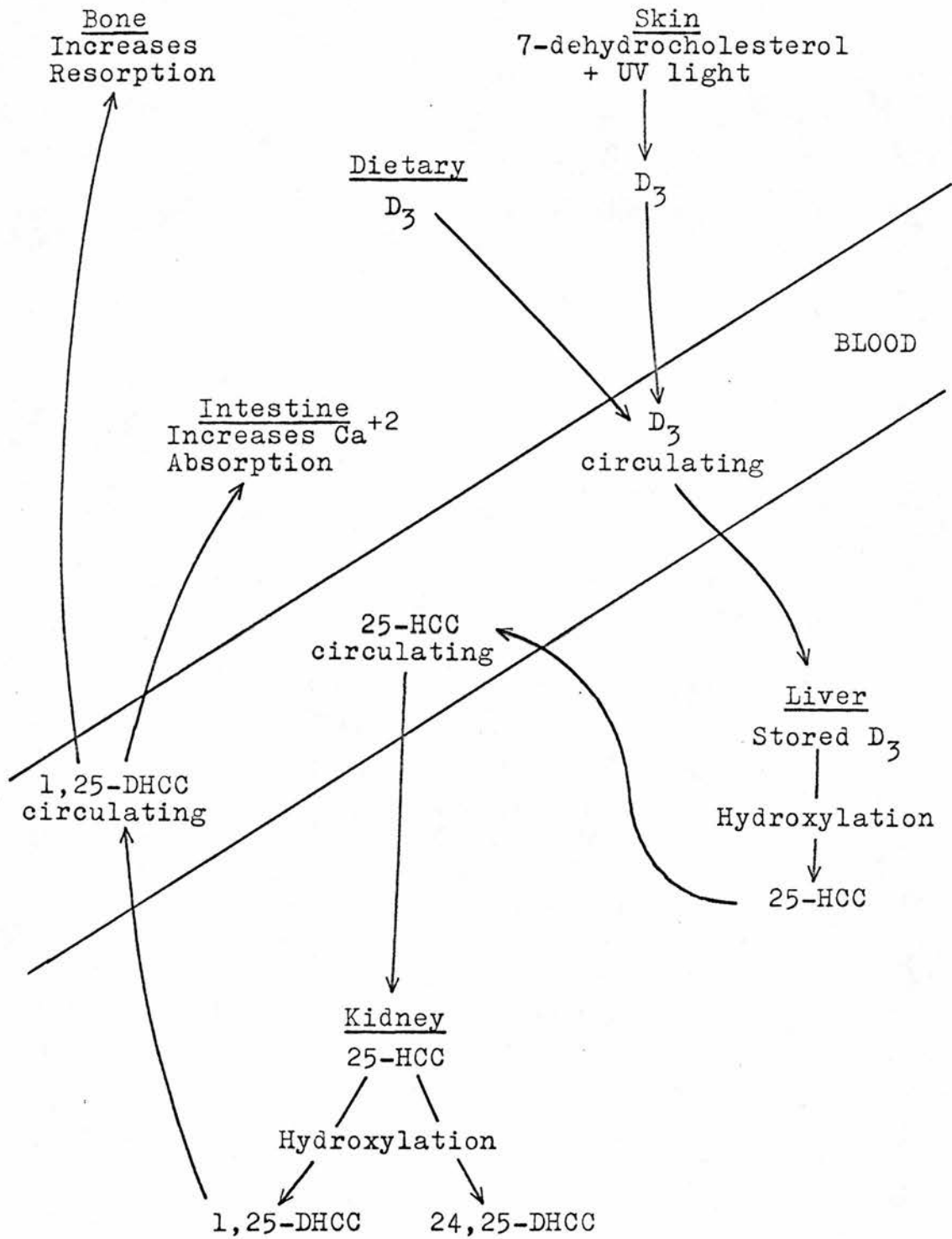
An analogue of vitamin D, which may bypass the renal hydroxylating mechanism, has been synthesized. This analogue, 1- α -hydroxycholecalciferol (1- α -HCC), is fortunately relatively simple to produce (Harrison et al 1974).

Both short and long term studies have been performed on patients with chronic renal failure using various dosages of 1- α -HCC. 10 μ g daily for a few days was found to increase calcium absorption two to three-fold, raise the serum calcium and reduce the serum alkaline-phosphatase (Chalmers et al 1973). 25 μ g daily was shown to decrease resorption from bone in renal patients and to increase it in patients with normal renal function (Peacock et al 1974).

Longer term studies were performed using much lower dosages and the bone calcium was monitored by neutron activation analysis. Three patients, all on dialysis for

FIGURE 7.3

Production and Effects of Vitamin D Metabolites



about five years, were followed over 18 months before treatment with $1-\alpha$ -HCC began; a further three studies were made at intervals of one month after the start of therapy. The dialysate calcium was 1.5 mmol.l^{-1} and two patients received $2 \mu\text{g}$ and the other $1 \mu\text{g}$ $1-\alpha$ -HCC daily. Significant increases in calcium were observed ($p < 0.001$) in the hand in all three patients (Catto et al 1974).

A study was also carried out on four patients over a period of 10 to 12 months. They were given 0.5 to $2 \mu\text{g}$ $1-\alpha$ -HCC daily with the dialysate calcium 1.6 mmol.l^{-1} (0.8 mEq.l^{-1}). Two patients showed significant biochemical, radiological, histological and total body calcium changes corresponding to increased calcium uptake in bone. The other two patients showed no improvement and one of these showed signs of deterioration (Naik et al 1976).

The patient studies using $1-\alpha$ -HCC have not sufficiently evaluated the effect on bone over a long time period. Catto (1975) only showed an increase over a three month period in bone and this was in only three patients without a control group. In the study over a longer time period however (Naik et al 1976), the results were inconclusive, partly due to the structure of the study.

A study was set up in Edinburgh, in conjunction with the medical renal unit, to use the ^{252}Cf apparatus to evaluate $1-\alpha$ -HCC. Twenty-one patients aged 26 - 58 (mean 41 years) were chosen for the study, being the complete population of patients on home dialysis never having received $1-\alpha$ -HCC. They had been established on haemo-

dialysis for 2 - 11 years (mean 4.5 years) and prior to the study, dialysis in all patients was conducted with a dialysate calcium concentration of 1.75 mmol.l^{-1} .

The twenty-one patients were randomly allocated to one of three groups. Group 1, the control group, continued treatment with a dialysate calcium concentration of 1.75 mmol.l^{-1} . Two patients, however, failed to attend leaving only five patients in this group. Groups 2 and 3 contained seven patients each in whom the dialysate calcium concentration was reduced to $1.375 \text{ mmol.l}^{-1}$. In addition, the patients in group 3 were given $1\text{-}\alpha\text{-HCC}$ in an initial dose of $2 \mu\text{g}$ daily by mouth. No other aspects of treatment were altered in any group.

Neutron activation analysis measurement of both fore-arms was performed at 0, 8 and 16 months from the start of the study. Densitometry measurements of the non-fistula arm were performed at the same time but due to an error, results could only be obtained at 8 and 16 months. Metacarpal indices were determined at 0 and 8 months.

All patients completed the study with the exception of one patient in group 2 (Mrs.S.D.) whose dialysate calcium concentration had to be increased after the 8 month measurement because of excessive calcium loss.

7.3 Results of the Renal Study

The results from the patients are given in Tables 7.1a, b and c, the figures being the percentage change from time zero. The calcium counts from neutron activation

TABLE 7.1a

Percentage Change in Neutron Activation Analysis
Measurements of the Non-Fistula Arm

Time Period	0 to 8 months	8 to 16 months	0 to 16 months
1. Controls			
R.C.	-3.98	-4.65	-8.63
W.H.	-0.22	-5.73	-5.95
I.R.	+2.22	+0.77	+2.99
J.R.	-5.11	+1.30	-3.81
T.W.	-1.42	-4.45	-5.87
2. Low Ca			
J.B.	+2.48	-2.09	+0.39
* S.D.	-8.98	+7.32	-1.66
T.D.	+1.55	+0.05	+1.60
D.F.	+0.28	+0.96	+1.24
W.I.	+2.71	+2.97	+5.68
R.M.	+11.73	-8.26	+3.47
M.W.	+4.09	-3.25	+0.84
3. Low Ca and I α			
G.A.	+7.73	-2.82	+4.91
J.E.	+14.86	+4.93	+19.79
C.F.	+15.68	+1.67	+17.35
W.F.	+11.84	-5.87	+5.97
J.M.	+4.07	+4.17	+8.24
C.M.	+4.99	-3.15	+1.84
I.M.	+5.64	-0.18	+5.46

TABLE 7.1b

Percentage Change in Neutron Activation Analysis
Measurement of the Fistula Arm

Time Period	0 to 8 months	8 to 16 months	0 to 16 months
1. Controls			
R.C.	3.38	-11.07	-7.69
W.H.	-1.02	-1.63	-2.65
I.R.	+6.97	-8.52	-1.55
J.R.	+4.72	-1.36	+3.36
T.W.	-2.12	-12.75	-14.87
2. Low Ca			
J.B.	+3.59	-0.59	+3.00
* S.D.	-5.16	+2.07	-3.09
T.D.	+13.42	-11.85	+1.57
D.F.	+4.42	-3.67	+0.75
W.I.	+3.45	+1.56	+5.01
R.M.	+11.52	-9.49	+2.03
M.W.	+7.18	+2.53	+9.71
3. Low Ca and I α			
G.A.	+8.18	-0.26	+7.92
J.E.	+7.84	-1.35	+6.49
C.F.	+7.15	+8.90	+16.05
W.F.	+3.19	-3.81	-0.62
J.M.	-4.85	-0.62	-5.47
C.M.	+1.57	-0.45	+1.12
I.M.	+13.25	-5.65	+7.60

TABLE 7.1c

Percentage Change in Densitometry and Metacarpal
Indices Measurements

Time Period	<u>Densitometry</u>	<u>Metacarpal Index</u>	
	Non-Fistula	Non-Fistula	Fistula
	8 to 16 months	0 to 8 months	0 to 8 months
1. Controls			
R.C.	-14.30	+7.30	-1.40
W.H.	-4.98	+8.72	+4.20
I.R.	+2.41	-3.94	-3.55
J.R.	-1.63	-	-
T.W.	+3.93	-10.13	-54.75
2. Low Ca			
J.B.	-3.58	-14.62	-16.69
* S.D.	+1.94	-6.06	+2.19
T.D.	-6.52	-	-
D.F.	-8.91	-	-
W.I.	+14.43	+12.32	-0.24
R.M.	-2.47	-6.89	+1.76
M.W.	-	-6.79	-19.36
3. Low Ca and I α			
G.A.	+5.54	+13.04	-9.54
J.E.	-0.08	-5.95	+5.76
C.F.	+4.98	-2.00	-7.26
W.F.	-6.49	+74.15	-16.31
J.M.	+1.49	+81.98	+3.89
C.M.	-4.43	+0.63	-6.28
I.M.	-0.10	-6.35	-2.19

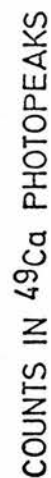
analysis measurements at time 0 are shown in Figure 7.4. This illustrates the wide variation in calcium from one patient to another. This three-fold variation between the maximum and minimum was due not only to the size and calcium loss in the patient but also to the design of the apparatus. The fact that there was an air gap between the forearm and the reflectors and premoderators, unlike the water bath apparatus, meant that soft tissue round the bone affected the total calcium counts. Patients of small stature will in general have correspondingly less soft tissue which meant less "reflector" around the bone and hence a lower calcium count.

Also noticeable in Figure 7.4 is a difference between the arms of each patient. It is not possible to say whether the tendency to have larger calcium levels in the right forearm was due to dominance of that arm in eighteen out of nineteen patients, or the absence of a fistula in the right arm in sixteen out of nineteen patients.

The changes in calcium in the non-fistula arm over the initial 0 to 8 month period is shown in Figure 7.5, as measured by neutron activation analysis. It can be seen that the calcium levels in patients in group 3, who received 1- α -HCC, increased to a much larger extent than the other two groups. Because of the relatively small number of patients in each group, non-parametric statistical methods are most suitable to analyse the data.

Taking the groups in pairs and using the Mann-Whitney test (Snedecor and Cochran 1967) the significance of the difference between group 3 and groups 1 and 2 was $p < 0.01$

FOREARM Ca ACTIVATION IN DIALYSIS PATIENTS



and $p < 0.03$ respectively. The difference between group 1 and group 2 was however not significant ($p > 0.10$).

These results were in agreement with the biochemical findings (Winney et al 1977) where there was a significant increase in plasma calcium ($p < 0.05$) only in group 3. The metacarpal indices showed no significant differences between the groups although large increases were recorded in two patients (J.M. and C.M.), both of whom were in group 3.

No significant differences exist between the groups when the fistula arm is considered (Fig. 7.6). However the differences between the changes in the two arms is very interesting. The difference between the changes in either forearm is shown in Figure 7.7. Using the Wilcoxon signed rank test on the twelve patients not receiving $1-\alpha\text{-HCC}$, the difference between changes in the two arms was highly significant ($p < 0.01$). The fact that the cimino fistula used for haemodialysis substantially increased venous pressure and therefore might be expected to protect against bone loss, seemed a possible explanation for this result (MacPherson 1977).

The calcium measurements over the next 8 month period showed a different pattern from the first 8 month period. The patient who was removed from the study (Mrs.S.D.) was also measured at 16 months and the increased dialysate calcium was found to increase significantly the forearm calcium level. Figure 7.8 shows the percentage change measured in the non-fistula arm by activation analysis, and no significant differences exist between the groups. The mean calcium change in the group receiving $1-\alpha\text{-HCC}$ is

Figure 7.5

Calcium changes in renal patients

Non-fistula arm - 0 to 8 months

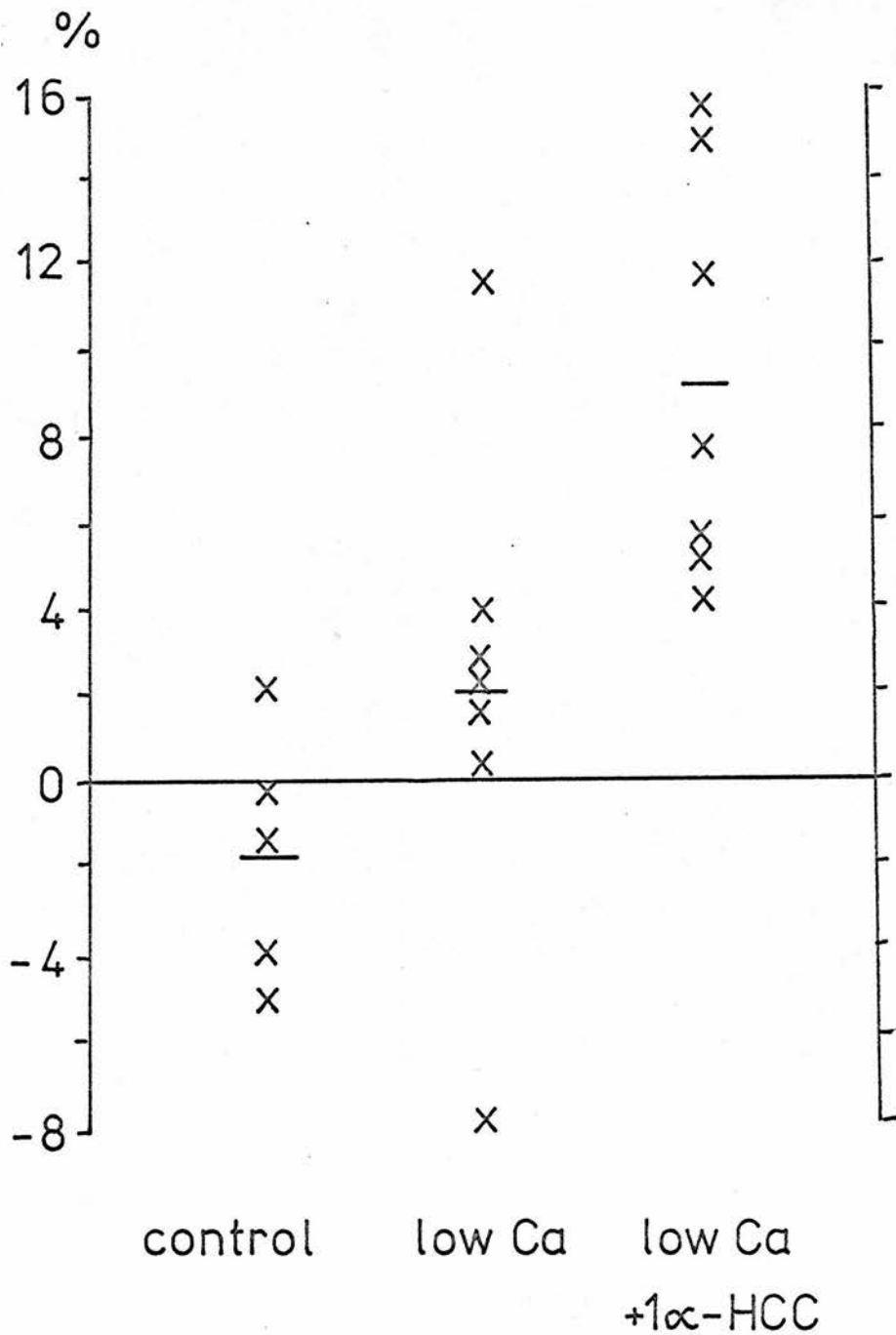


Figure 7.6

Calcium changes in renal patients,

Fistula arm - 0 to 8 months

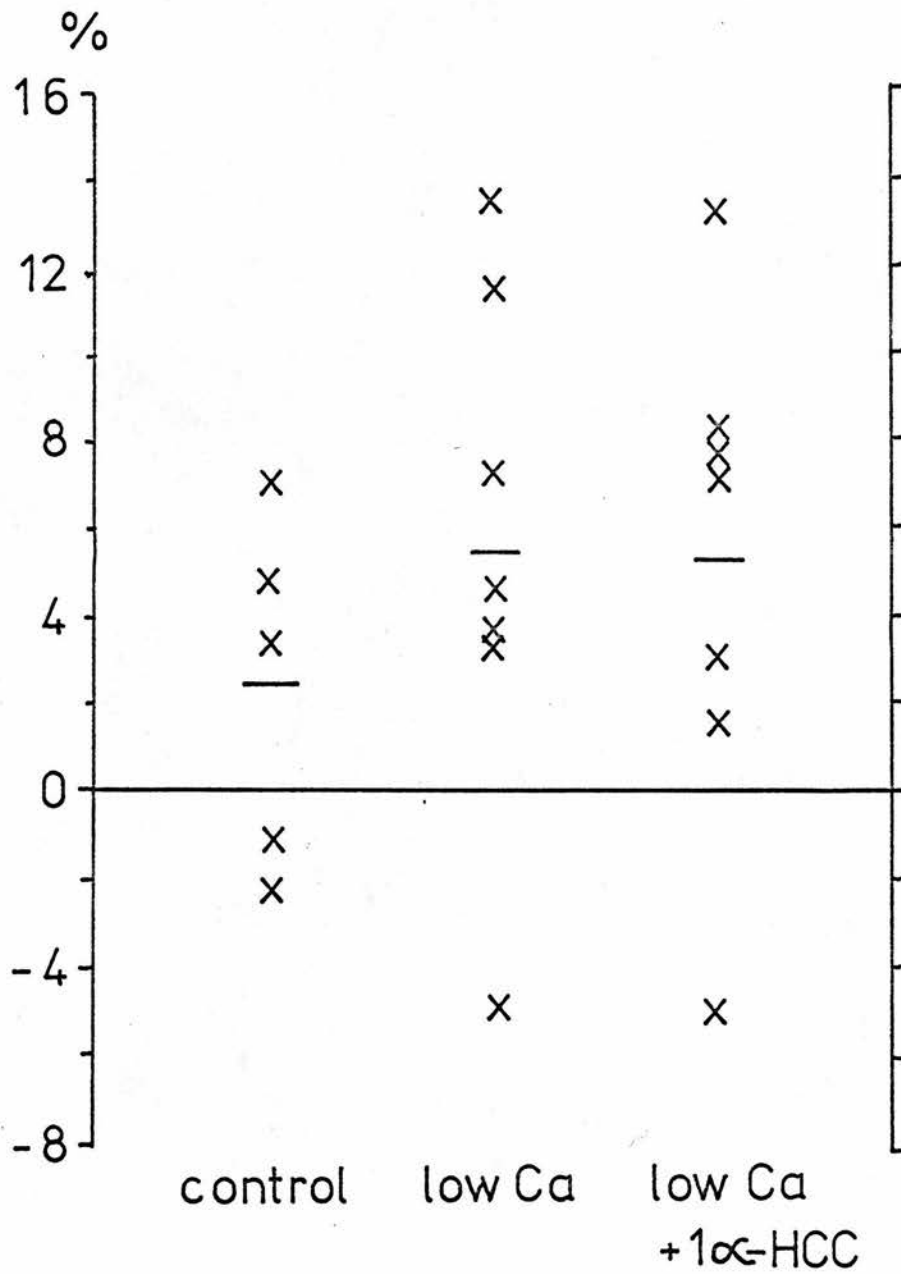
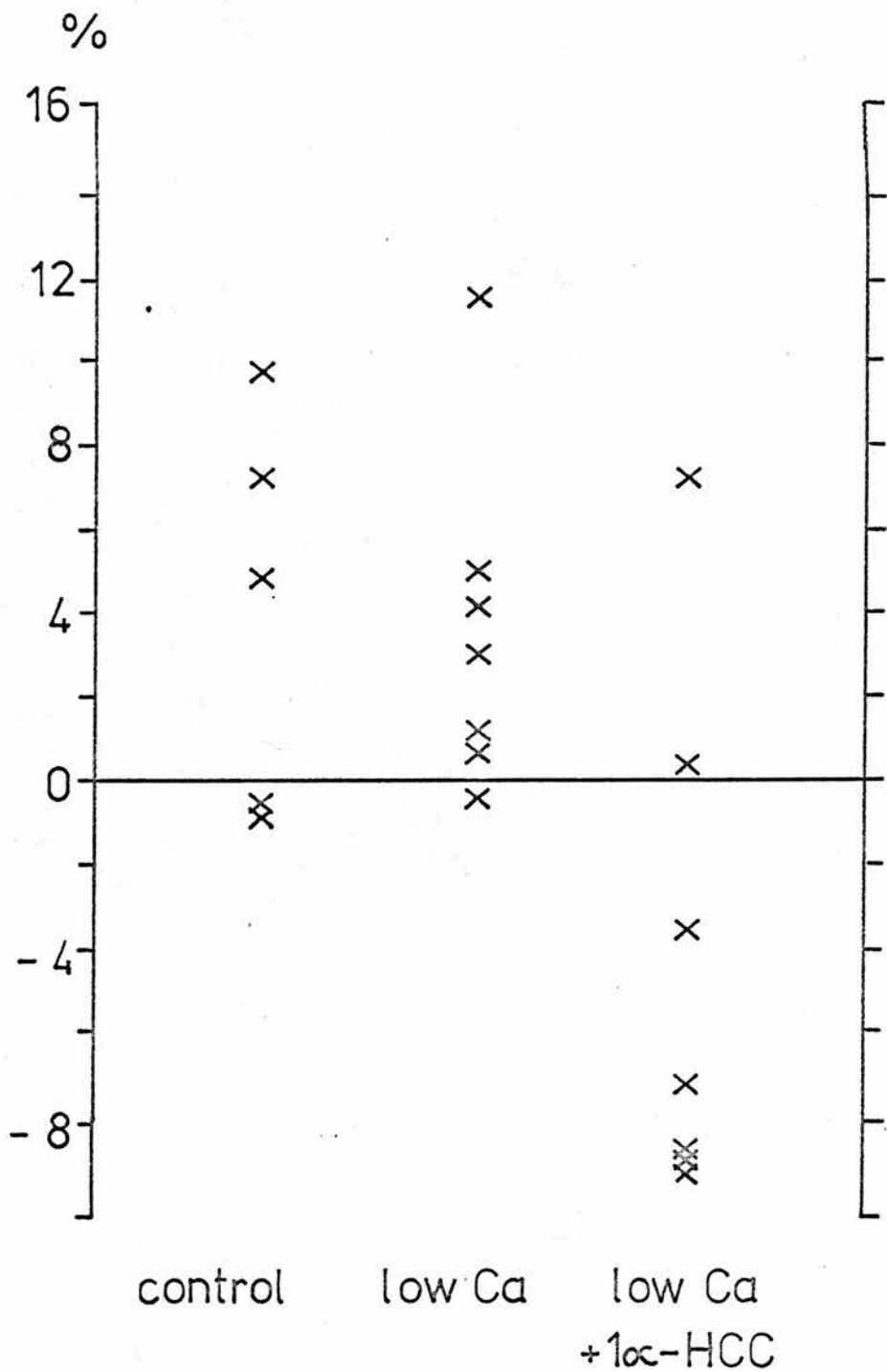


Figure 7.7

Renal patients 0 to 8 months

% change in fistula arm minus

% change in non-fistula arm



only -0.18% over the second 8 month period compared with +9.26% over the first. Comparing the data in Figures 7.8 and 7.5 the response in each group, taking the non-fistula arm, over the two time periods, is only significantly different in group 3 ($p < 0.01$) which was receiving 1- α -HCC.

Assuming that the non-fistula arm was most representative of overall calcium changes in the patient, it was seen that 1- α -HCC increases the calcium in bone significantly compared to controls. However this increase was not continuous in the long term and 1- α -HCC had no effect on the patient over a period 8 to 16 months after the start of treatment.

Changes in the fistula arm (Fig. 7.9) were lower over the second 8 month period than over the first (Fig. 7.6), significantly so in group 2 ($p < 0.03$). The difference between changes in the fistula arm and the non-fistula arm were also significant over 8 to 16 months ($p < 0.05$) but in the opposite direction to the first 8 months (Fig. 7.10). This result casts doubt on the proposed explanation of the effect noted over the first 8 month period.

It was not possible to compare patients on different dialysate calcium levels not receiving 1- α -HCC, with any degree of significance. However, inspection of the data for both arms over the first time period (Figs. 7.5, 7.6), suggested that reducing the bath calcium increased the calcium in the bone. As this effect was not present over the second 8 months (Figs. 7.8 and 7.9) it may have been due initially to the fact that the dialysate calcium was

Figure 7.8

Calcium changes in renal patients

Non-fistula arm- 8 to 16 months

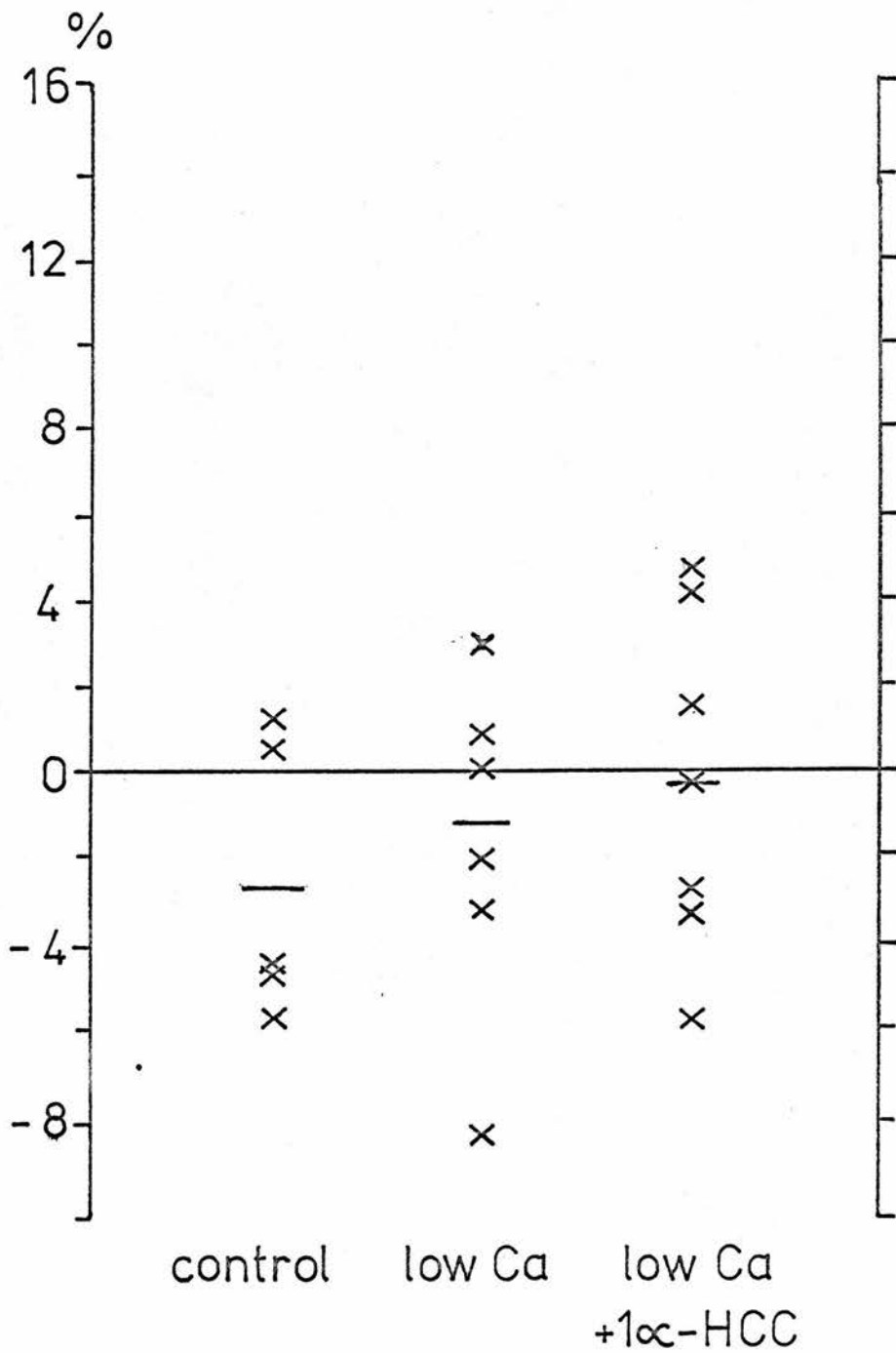


Figure 7.9

Calcium changes in renal patients

Fistula arm - 8 to 16 months

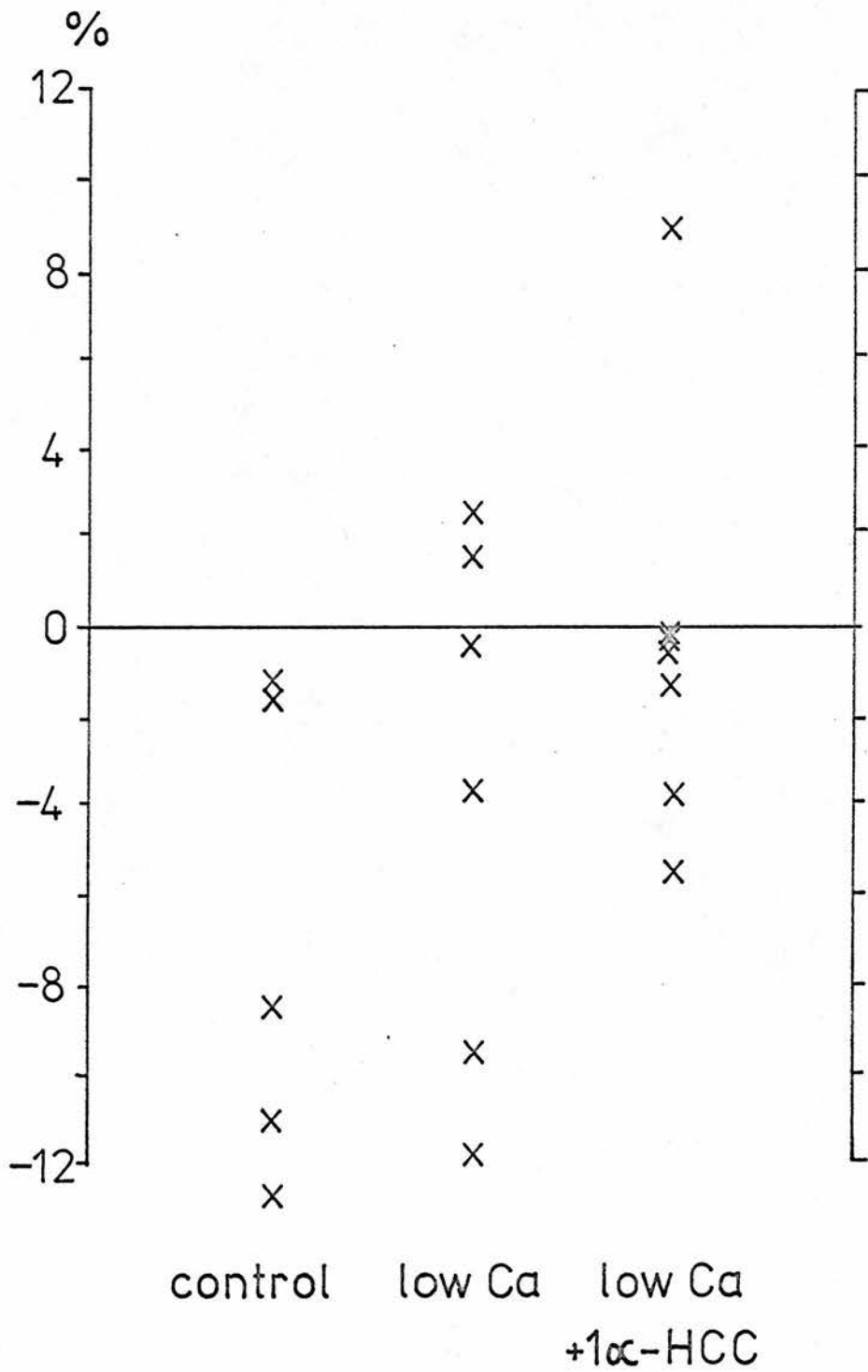
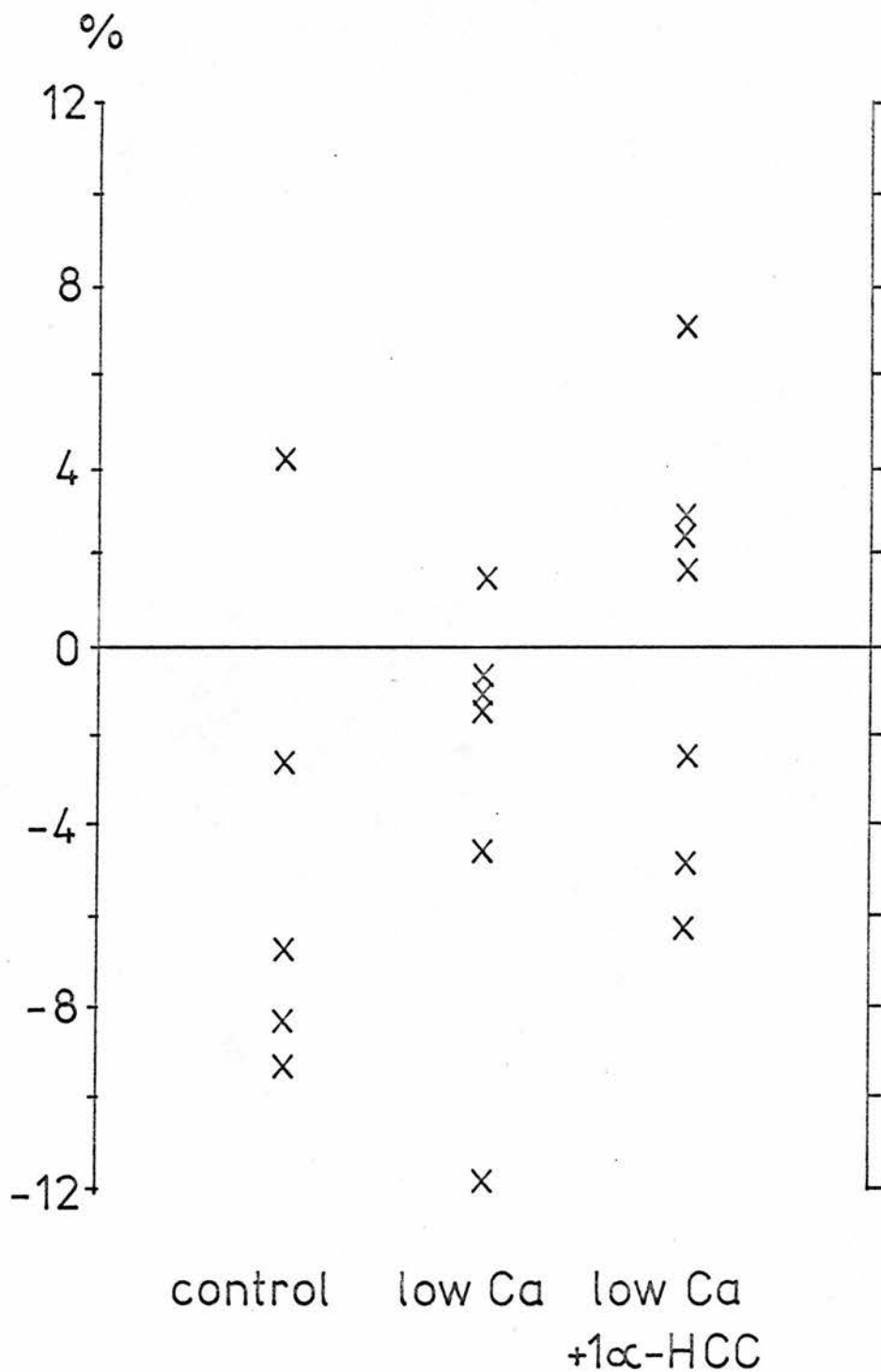


Figure 7.10

Renal patients. 8 to 16 months

% change in fistula arm minus

% change in non-fistula arm



changed rather than the level itself.

The densitometry results showed no change between the groups from 8 to 16 months. Comparisons will be made however between the densitometry and activation analysis results in a later section of this chapter.

7.4 Anticonvulsant Osteomalacia and its Treatment with Vitamin D

The effect of long term anticonvulsant therapy on the bone structure of epileptic patients has been investigated over the last ten years. Hypocalcaemia and radiological findings of rickets and osteopenia were reported in 15% of a German paediatric outpatient epileptic population (Kruse 1968). An even higher proportion has been reported; 30% for institutionalised children and 23% for adults (Richens and Rowe 1970). These figures may be high because the patients were in institutions and Shaefer (1973) concluded that the proportion of epileptic patients with some form of bone disease was between 15 to 25%.

Experiments have been performed using the two most common anticonvulsant drugs, diphenylhydantoin (phenytoin) and phenobarbital. Caspary (1972) reported inhibition of intestinal calcium transportation in rats by phenytoin in rat duodenum. Work on patients and rats with phenobarbital led Hahn (1972) to conclude that the resultant osteomalacia may be the result of an accelerated conversion of vitamin D and its active metabolite 25-HCC, to polar inactive metabolites by drug induced liver enzymes.

Studies on 48 combined drug recipients and 38 controls

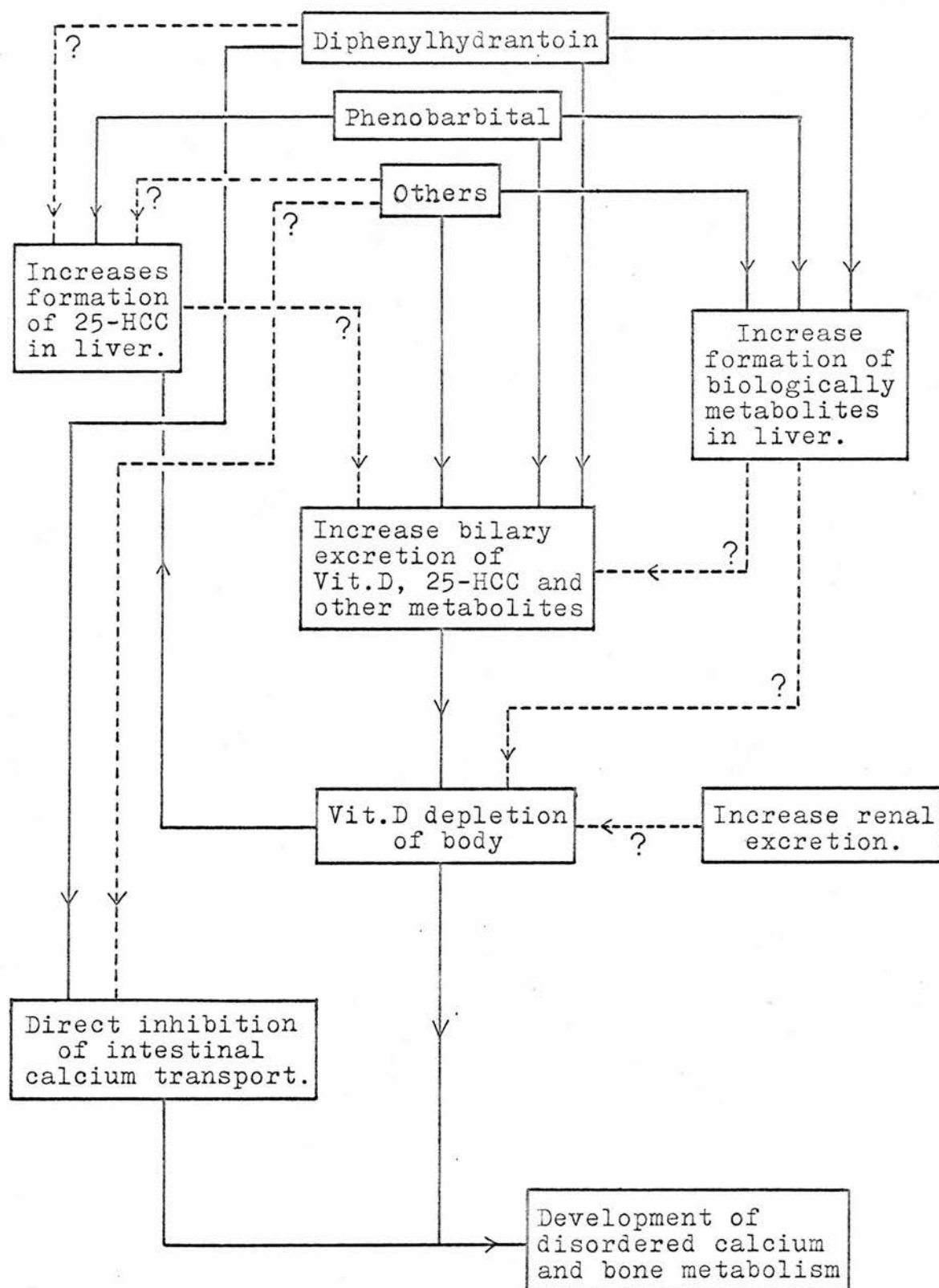
showed significant changes ($p < 0.01$) in biochemical values; plasma calcium and 25-HCC decreased while hepatic and bone alkaline phosphatase both increased (Hahn et al 1975).

Histological studies on 60 patients on phenytoin showed an increase in the level of demineralized bone, consistent with the diagnosis of osteomalacia. The vitamin D intake of the patients varied from 35 to 980 IU daily and the biochemical values agreed with the study mentioned previously (Melsen and Mosekilde 1976). A diagrammatic representation of the effects of anticonvulsant therapy is given in Figure 7.11.

Having established the effect on calcium metabolism of long term treatment with anticonvulsant drugs, vitamin D therapy was investigated. Using densitometry to measure the bone mineral content (B.M.C.), Christiansen and Rødbro (1976) investigated the effect of various types of vitamin D on the bone calcium. In their first study (Christiansen et al 1973) the effect of vitamin D₂ and placebo was compared. 226 patients on anticonvulsant drugs were randomly divided into two groups and given either 2,000 IU/day D₂ plus 390 mg Ca/day, or a placebo plus 415 mg Ca/day. This was continued for 3 months. No change in the B.M.C. was noted in the placebo group but an average increase of 4% was noted in the group receiving vitamin D₂. The respective incidence of raised serum alkaline phosphatase and hypocalcaemia was 12% and 43%. The authors also stated that a correlation was found between the B.M.C. and the "load" of anticonvulsants, i.e. the dose ($r = 0.24$) and the length of treatment ($r = 0.26$).

FIGURE 7.11

Effects of Anticonvulsant Therapy



The action of vitamin D₃ and 25-HCC was investigated in fifty-four patients who had received anticonvulsant therapy for at least one year (Christiansen et al 1975). Nine patients were placed in each of the following six treatment groups: 200, 100, 50 µg D₃ daily and 40, 20, 10 µg 25-HCC daily. This was given over a period of 12 weeks with an additional 500 mg/day calcium by mouth. No change was noted in the B.M.C. in either group. However increases were seen in the serum calcium in the 50 µg D₃ group ($p < 0.01$) and in the 100 µg D₃ and 40 µg 25-HCC groups ($p < 0.02$).

In a review of their work, Christiansen and Rødbro (1976) concluded that the B.M.C. of epileptics on anticonvulsant therapy was about 88% of the normal value. The B.M.C. could be stabilized with 4,000 IU (100 µgm) D₂ daily for 4 to 5 months then 1,000 IU D₂ daily to maintain this level.

Conflicting evidence was available from two other sources. 50,000 IU/day of calciferol without calcium supplement was given to ten epileptic and ten normal patients for a six month period (Linde et al 1972). Gamma ray densitometry of the elbow and foot showed no significant change in the bone density over this period suggesting that vitamin D₂ did not affect anticonvulsant osteomalacia.

The beneficial effect of vitamin D₃ was shown by Peterson (1976). Thirty-six epileptic patients were studied, eighteen with and eighteen without clinical symptoms of drug-induced osteomalacia. Balance studies showed that 975 IU/day of D₃ was required to maintain the osteomalacic

group in positive calcium balance, whereas the control group required 380 IU/day. This difference was stated to be significant at $p < 0.001$ suggesting that vitamin D_3 was a possible treatment for anticonvulsant osteomalacia.

To evaluate the effect of D_2 and D_3 on anticonvulsant osteomalacia the following study was set up. Thirty-four patients between 21 and 50 years of age and who had been on anticonvulsant therapy for at least 5 years were randomly allocated to one of three groups. Group 1, the control group, were given a placebo, group 2 were given 100 μg (4000 IU)/day of vitamin D_2 and group 3 the same dose of vitamin D_3 . The vitamin D therapy was continued for 6 months and measurements were performed before the start and at the end of the treatment. Neutron activation analysis and densitometry measurements were performed on the non-dominant forearm, three measurements being done on each of the two occasions. Calcium absorption, using ^{45}Ca , and related biochemical tests were also performed and frequency of fits noted.

7.5 Results of Anticonvulsant Osteomalacia Study

The percentage change in the forearm over the six month period is shown in Table 7.2 for the thirty-two patients who completed the study. The results from neutron activation analysis (Fig. 7.12) show no difference between the three groups. The three groups showed a mean loss of 0.49%, 0.34% and 0.80% for 1 to 3 respectively. There was no significant difference between the three groups and

TABLE 7.2

Percentage Changes in Anticonvulsant Osteomalacia Study

<u>Patient</u>	<u>N.A.A.</u> <u>Change/6m</u>	<u>Densitometry</u> <u>Change</u>	<u>Biochemical</u> <u>Ca x PO₄</u> <u>Change</u>
<u>GROUP 1:Placebo</u>			
I.B.	3.62	1.90	6.44
Mrs. J.C.	1.04	-5.99	-3.50
M.C.	1.05	-3.95	-7.00
H.G.	-5.75	-13.01	18.53
L.H.	-2.44	-5.34	-19.61
Mr. C.H.	0.46	-7.35	-2.40
Mrs. C.H.	-2.31	-11.64	7.38
E.L.	2.77	-3.52	1.20
I.N.	1.46	3.79	-3.91
S.R.	-5.39	2.06	23.75
<u>GROUP 2:D₂</u>			
T.A.	-0.16	-0.52	11.90
Mrs. J.B.	-4.16	-12.90	5.77
Mr. J.C.	4.22	-7.35	-13.45
J.F.	-0.92	0.92	45.41
A.H.	-6.45	-5.42	-3.20
J.L.	0.70	0.29	-14.76
D.M.	1.27	-14.99	10.96
J.P.	4.50	3.87	-21.36
I.S.	3.27	11.23	1.36
C.W.	-5.66	-8.94	-3.79
<u>GROUP 3:D₃</u>			
Mr. J.B.	0.67	0.09	3.32
J.D.	-0.54	-0.57	7.34
E.F.	4.27	2.17	44.06
J.H.	-1.43	-10.11	5.45
G.L.	-0.38	3.22	-
Miss M.M.	-2.75	-1.53	-7.20
H.M.	0.35	-	21.56
Mrs. M.M.	0.63	1.58	21.76
A.T.	-6.01	-12.35	6.39
M.T.	-3.53	12.91	16.48
M.W.	-1.97	-15.90	12.65
H.S.	1.09	-4.37	-3.80

certainly nothing like the 4% increase in the D₂ group suggested by Christiansen (1973) even though the doses of vitamin D were doubled. The change in calcium, whether positive or negative was independent of the number of drugs and length of treatment. It was also independent of the degree of osteomalacia as determined by normalised neutron activation analysis measurements (see Section 7.8).

The results from the densitometry measurements are shown in Figure 7.13. It can be seen that there is a mean loss in each group though this loss was only significant in the control group ($p < 0.05$). There was no significant differences between any of the groups themselves.

From blood samples taken at 0 and 6 months the change in the product of plasma calcium and phosphate should give an indication of calcium changes. An increase would suggest a healing of any osteomalacia due to anticonvulsant therapy. Figure 7.14 shows the results of these values for the three groups. An increase was only seen in group 3 which was significantly different from zero ($p < 0.05$). The difference between the groups is not however significant.

The results from the anticonvulsant osteomalacia study are somewhat contradictory. Using neutron activation analysis no change was noted in any of the groups. In the few patients where significant changes ($p < 0.05$) were noted, these were not consistent with biochemical changes. Densitometry results showed a significant decrease in the placebo group but not any significant difference between the groups. Biochemical results suggest a significant increase in the

Figure 7.12
NAA changes in
anticonvulsant patients

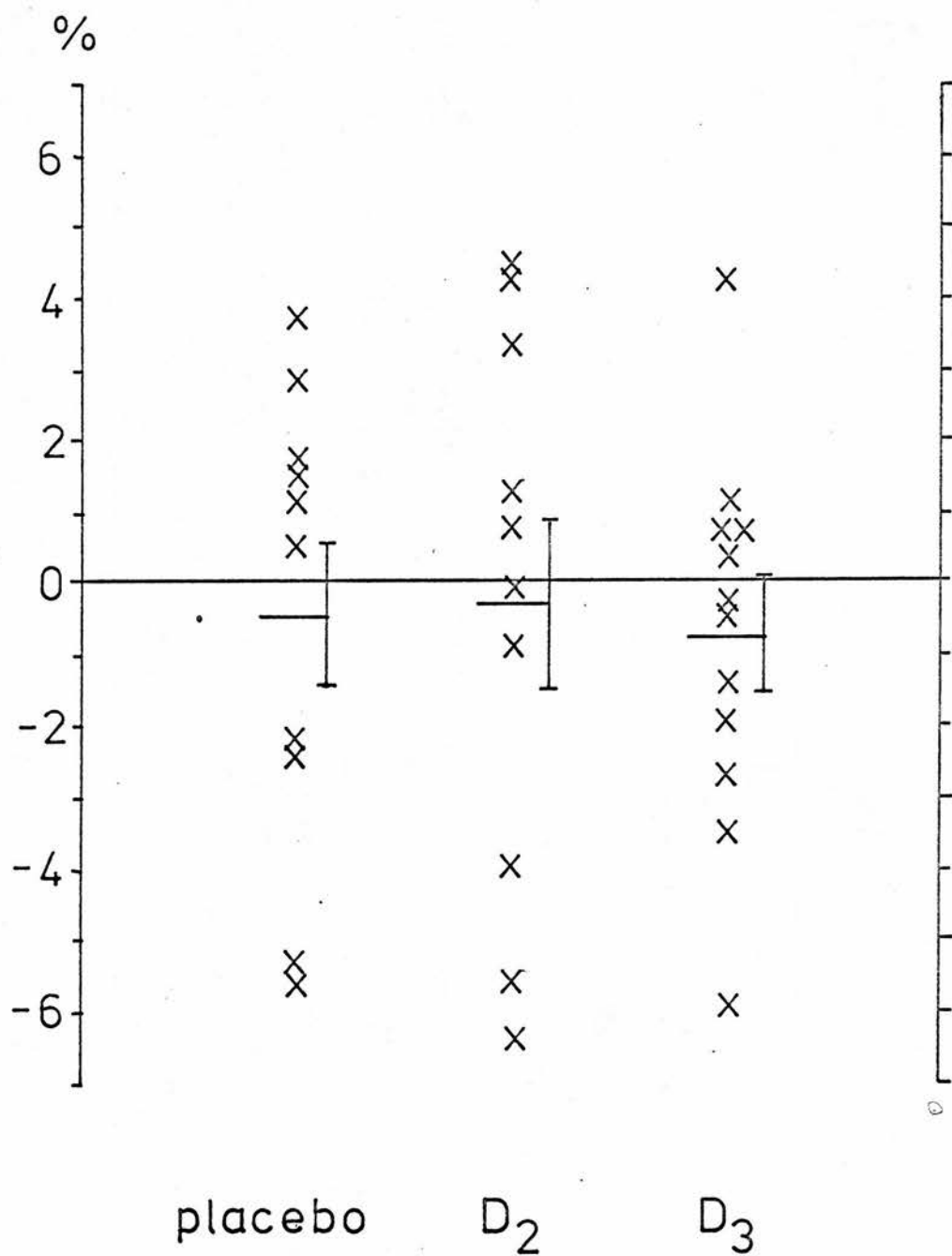


Figure 7.13

Densitometry changes in
anticonvulsant patients

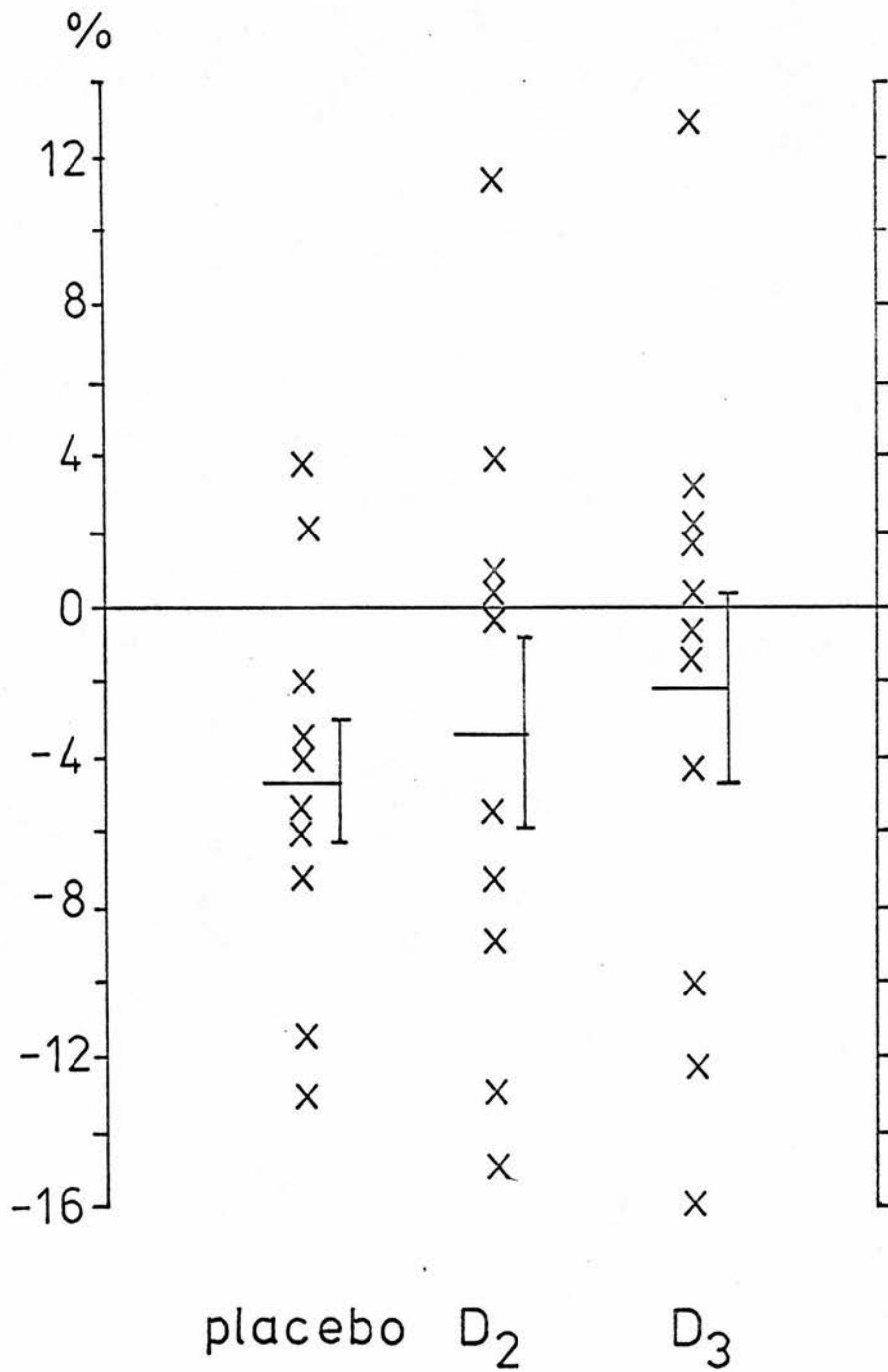
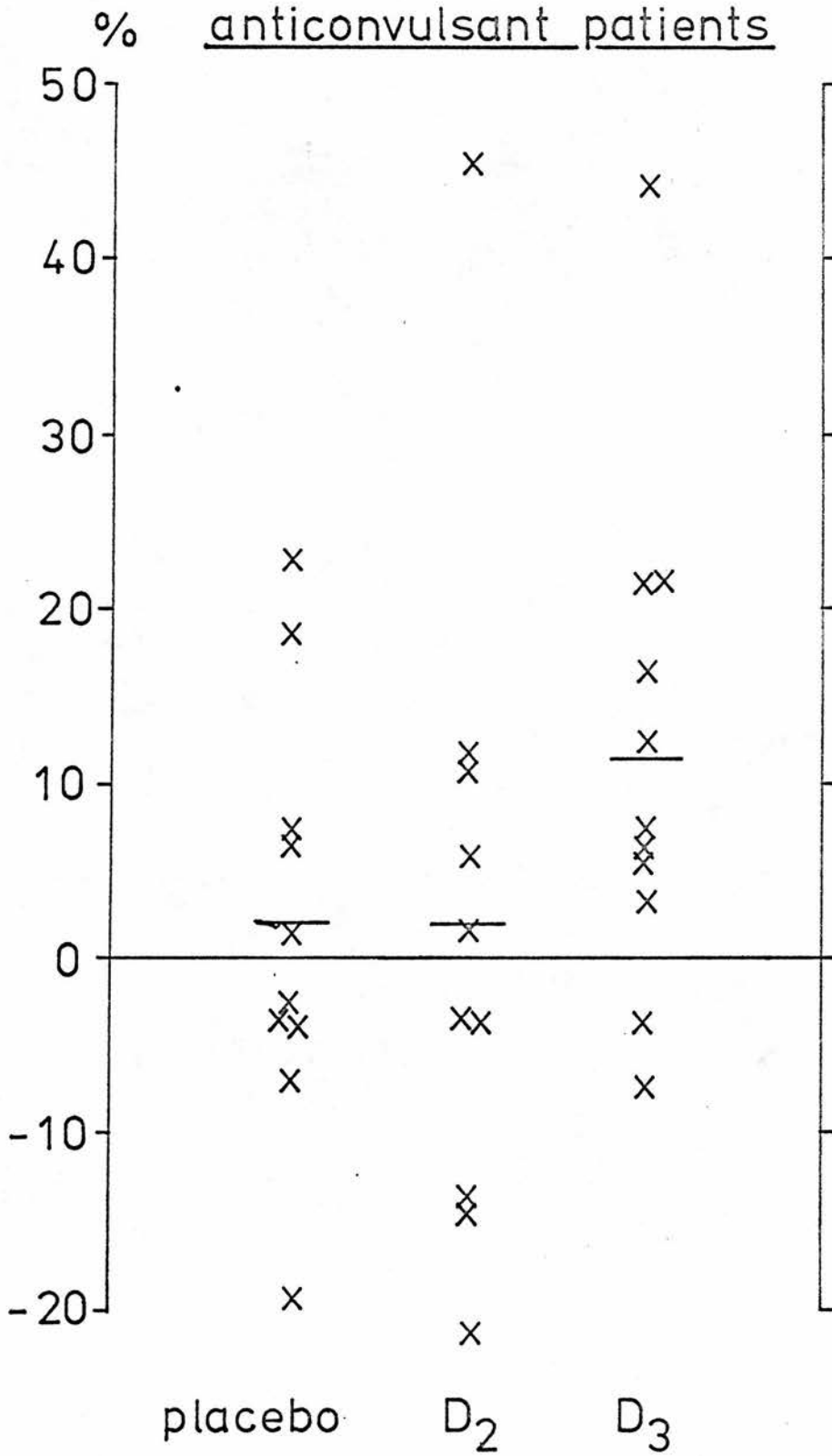


Figure 7.14

Plasma CaxP changes in
anticonvulsant patients



D₃ group although again no significant changes existed between the groups.

These results throw grave doubts on the efficacy of vitamin D treatment for anticonvulsant osteomalacia in the short term. A lack of any calcium change over 6 months from the neutron activation measurements would suggest that the benefits of vitamin D therapy do not justify the possible hazards to the patient and the extra medical supervision required.

7.6 Calcium Loss Associated with Lithium Carbonate Therapy

Lithium is widely used in the treatment of bipolar manic-depressive illness and in Edinburgh at present there are over 500 patients on long term treatment with lithium. The mode of action of lithium and many of its side effects have been investigated (Glen 1977) although as yet the question of calcium loss from patients taking lithium has not been fully answered.

Studies on rats showed that lithium appears to interfere with the distribution and handling of magnesium, calcium, sodium and potassium ions in brain, bone and muscle tissue (Birch and Jenner 1973). The rats were given lithium for a period of 28 days (1 mEq/Kg body weight/day) and in the bone tissue the lithium levels increased from 0.16 to approximately 1.00 mEq/Kg, while the calcium fell from 8891.0 to 8535.0 mEq/Kg, a loss of 4.0%. It could be seen from this that lithium was not simply replacing calcium ions

in bone on a one to one basis, as the calcium loss was much greater than the lithium increase. Previously Gotfredson and Rafaelson (1970) have shown that lithium-treated rats secreted significantly more calcium in urine than controls.

Lithium retention in bone has also been confirmed in man (Birch 1974) though not calcium loss from bone. Christensson (1976) reported six female patients who had been on lithium for 2 - 4 years. All developed hypercalcaemia after an average of one year without any other manifestations characteristic of hypercalcaemia such as subperiosteal resorption on skeletal X-rays. No evidence of increased urinary excretion of calcium was found though the serum calcium was significantly raised, the latter suggesting a favourable response to lithium (Glen 1977).

A loss of 15% of the bone density of patients treated chronically with lithium was verbally stated (Hullin et al 1977). These data never appeared in print, however, so doubt must be cast on their validity.

A study was set up in Edinburgh to monitor any calcium changes in patients about to commence lithium treatment for the first time. All patients between the ages of 21 and 65 were considered for the trial and were only excluded if they did not wish to participate or if their symptoms made the measurements impossible.

Neutron activation measurements of the non-dominant forearm were made before the start of treatment and after 6 months. The water bath and sets of three measurements were used on all occasions. Densitometry measurements of the

same arm were performed every 3 months when possible. Blood and 24 hour urine samples were also taken for analysis.

In addition to the information that would be obtained concerning the effect of lithium, this study produced the only set of "normal" neutron activation measurements, which were obtained from the patients before lithium therapy. A special note was made of any treatment in the past, such as ECT or imipramine (Faragalla and Flack 1970), which could have affected the "normal" calcium level in the bone.

When structuring the study it was not possible to include a control group because of the ethical problems of either withholding treatment or irradiating normals. Another problem in the study was the 50% dropout rate due to the cessation of lithium treatment or the refusal of the patient to return for the 6 month measurement.

7.7 Results of the Lithium Study

The results of the eight patients who completed the study are shown in Table 7.3 and in Figure 7.15. The mean loss of calcium by N.A.A., 2.47%, was not significant in the group as a whole though in two patients, M.P. and M.H., their individual calcium losses were significant.

This net loss of calcium, as measured by neutron activation analysis, was the opposite to the findings from densitometry. It can be seen that the bone mineral density increased, especially over the initial 3 month period. This average increase of 5.18% and 2.38% during the periods

0 - 3 m. and 0 - 6 m. respectively, could be due to the replacement of calcium by other elements, thus increasing the mineral density but reducing the calcium.

TABLE 7.3

Percentage Change in Patients Receiving
Lithium Carbonate Therapy

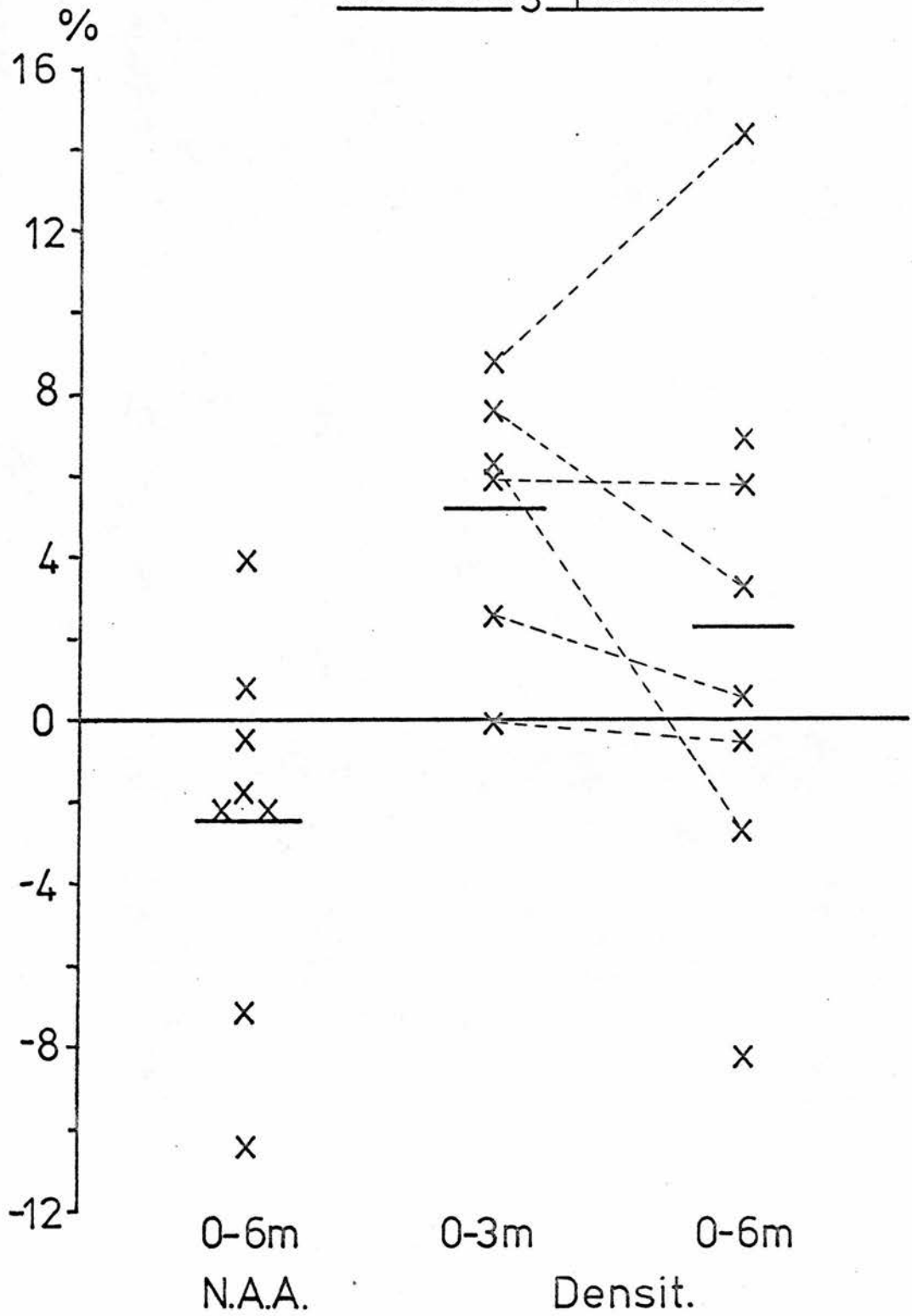
<u>Patient</u>	<u>N.A.A. % Change</u>	<u>Densitometry % Change</u>	
	6 m.	0 - 3 m.	0 - 6 m.
M.D.	3.88	2.65	0.51
F.D.	-1.90	-	-8.32
M.P.	-10.49 p<0.001	5.95	5.82
B.M.	0.71	7.57	3.12
B.S.	-2.04	-	6.93
M.H.	-7.35 p<0.05	6.20	-2.88
N.T.	-2.08	8.77	14.37
R.C.	-0.50	-0.07	-0.51

7.8 Absolute Calcium Levels

Although the emphasis of this research was concerned with sequential calcium measurements, the absolute levels of calcium in the patient groups are of interest. The absolute calcium levels in the forearm are proportional to the calcium counts if some correction is made for the patient's size. Thus a factor must be found to normalise the calcium counts and so reduce the variation in calcium counts between patients which is due purely to size.

Figure 7.15

% change by N.A.A. and densitometry
in LiCO_3 patients



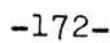
As stated previously, the initial set of three activation measurements on the lithium patients could be used as normals. A fairly good correlation ($r = 0.84$) was found to exist between the calcium counts corrected by the standard in fifteen patients and the cube of the patient's height. This normalisation factor was found to be better than Ht , Ht/Wt and Ht^3/Wt , where Ht and Wt were the patient's height and weight respectively. Thus all the initial measurements of patients using the water bath were normalised by dividing by the height cubed.

In addition to looking at all the lithium and anti-convulsant patients, data were available from patients suffering from thyrotoxicosis. Initial measurements had been made on ten patients but final measurements on these patients would not be completed until towards the end of 1978. The results of fifty-six patients expressed as calcium counts \times std counts⁻¹ \times Ht^{-3} are shown in Figure 7.16. The values from the patients on anticonvulsant drugs are in three columns corresponding to the length of treatment.

The coefficient of variation of the values of patients in the "normal" group was 12.19%. This shows that a fairly wide range exists in the normal bone values and thus would be of little use as a diagnostic procedure.

Bone loss is associated with thyrotoxicosis and from the normalised data, the mean of the calcium was probably significantly lower ($p < 0.10$) by 11.9% than in the normal group. This suggests that some degree of osteodystrophy was present so any trend back to normal levels should be

Normalised calcium measurements



registered by subsequent activation measurements.

The data from the anticonvulsant group, however, were not significantly different from normal. No difference existed between any of the three different groups in which the anticonvulsant patients' data were subdivided. This was unexpected as any degree of osteomalacia should be expressed as a lowered value of the mean calcium counts. If no osteomalacia were present in this group of patients, as the results in Figure 7.16 suggest, it would help to explain why no change of calcium, with vitamin D therapy, was measured by neutron activation analysis. Also no difference was noted between the three groups of anticonvulsant data in Figure 7.16, showing that the "load" of anticonvulsant drugs had no effect on the absolute calcium level. The same result was obtained with the densitometry values, normalised by the width of the radius.

7.9 Comparison of Neutron Activation Analysis with Other Techniques

It has been shown that a good correlation exists between calcium counts, as measured by activation analysis, and densitometry of the radius (see Section 1.6). The good correlation was largely due to the fact that both measurements reflect the size of the patient. In this comparison of different methods it is changes over a time period that will be dealt with.

The changes between activation analysis and densitometry were correlated for the renal patients, over the 8 to 16 month period, and for the anticonvulsant patients

(Figures 7.17 and 7.18 respectively). The correlation coefficients both showed a reasonable correlation, $r = 0.41$ ($p < 0.10$) and $r = 0.38$ ($p < 0.05$). The degree of correlation was higher than that found by Aloia (1975) and Cohn (1976) who compared changes in densitometry with changes in whole body neutron activation analysis.

This level of correlation between the two methods, measuring changes at the same site, showed that densitometry was not a particularly accurate method for measuring calcium changes in the bone. In addition there were several measurements of changes of around $\pm 15\%$ which was unrealistically large. The range of changes as measured by densitometry was over twice that measured by activation analysis, suggesting that the latter was more accurate and reliable.

No correlation was found with biochemical values in the anticonvulsant patients. The changes in the $\text{Ca} \times \text{PO}_4$ product, obtained from blood samples and giving an indication of the degree of healing of osteomalacia, were correlated with both activation analysis and densitometry changes and values of $r = -0.11$ and $r = 0.06$ respectively were obtained. To check that the $\text{Ca} \times \text{PO}_4$ product was not simply reflecting the changes in calcium absorption from the gut due to vitamin D, the changes were correlated with changes in Ca^{45} absorption and no correlation was found ($r = 0.07$).

As stated earlier, the activation results suggested not only that vitamin D_2 or D_3 had no effect, but that there may have been no osteomalacia present in the first

Figure 7.17

NAA changes v. Densit. changes
renal patients - 8 to 16 months

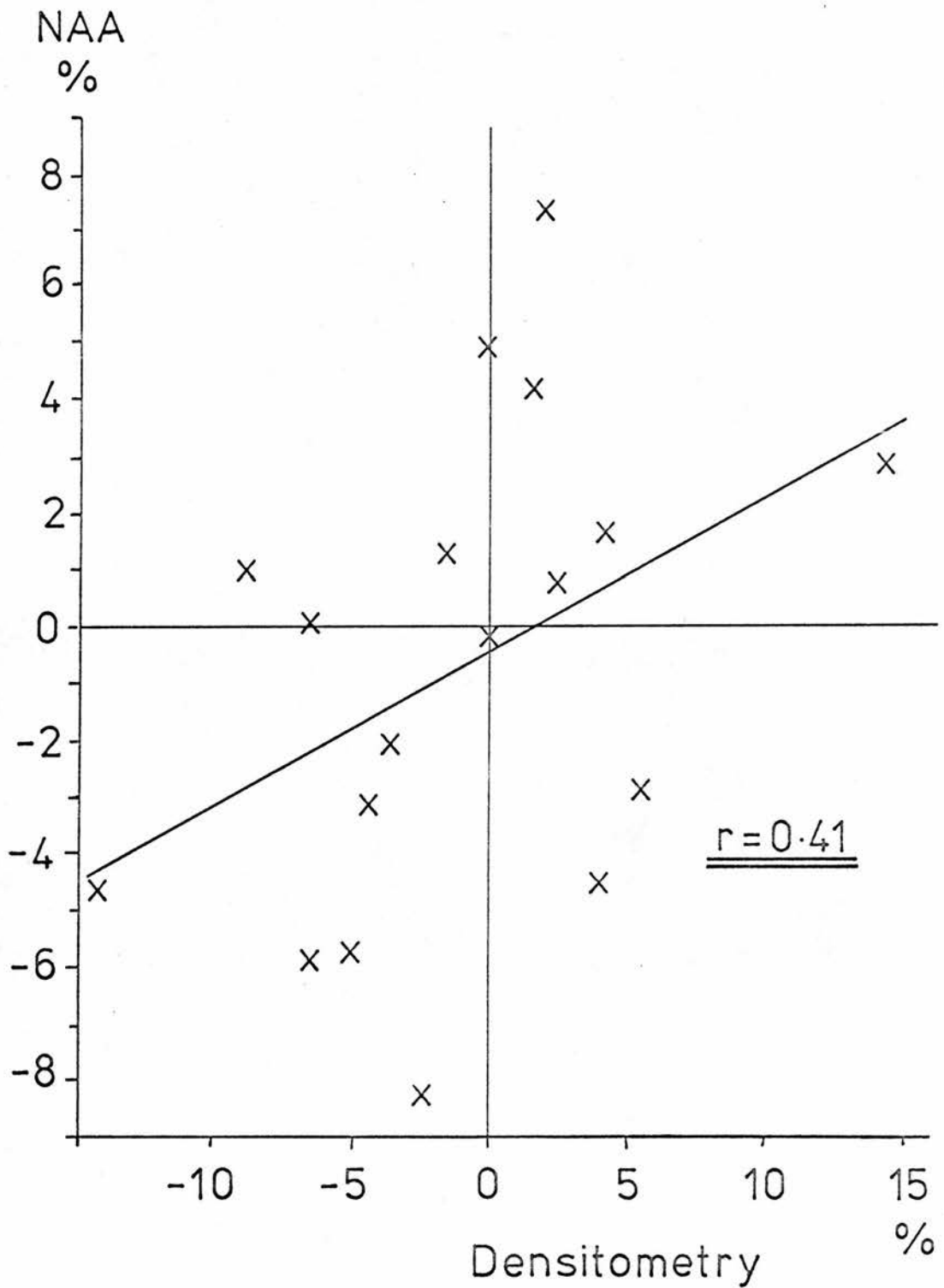
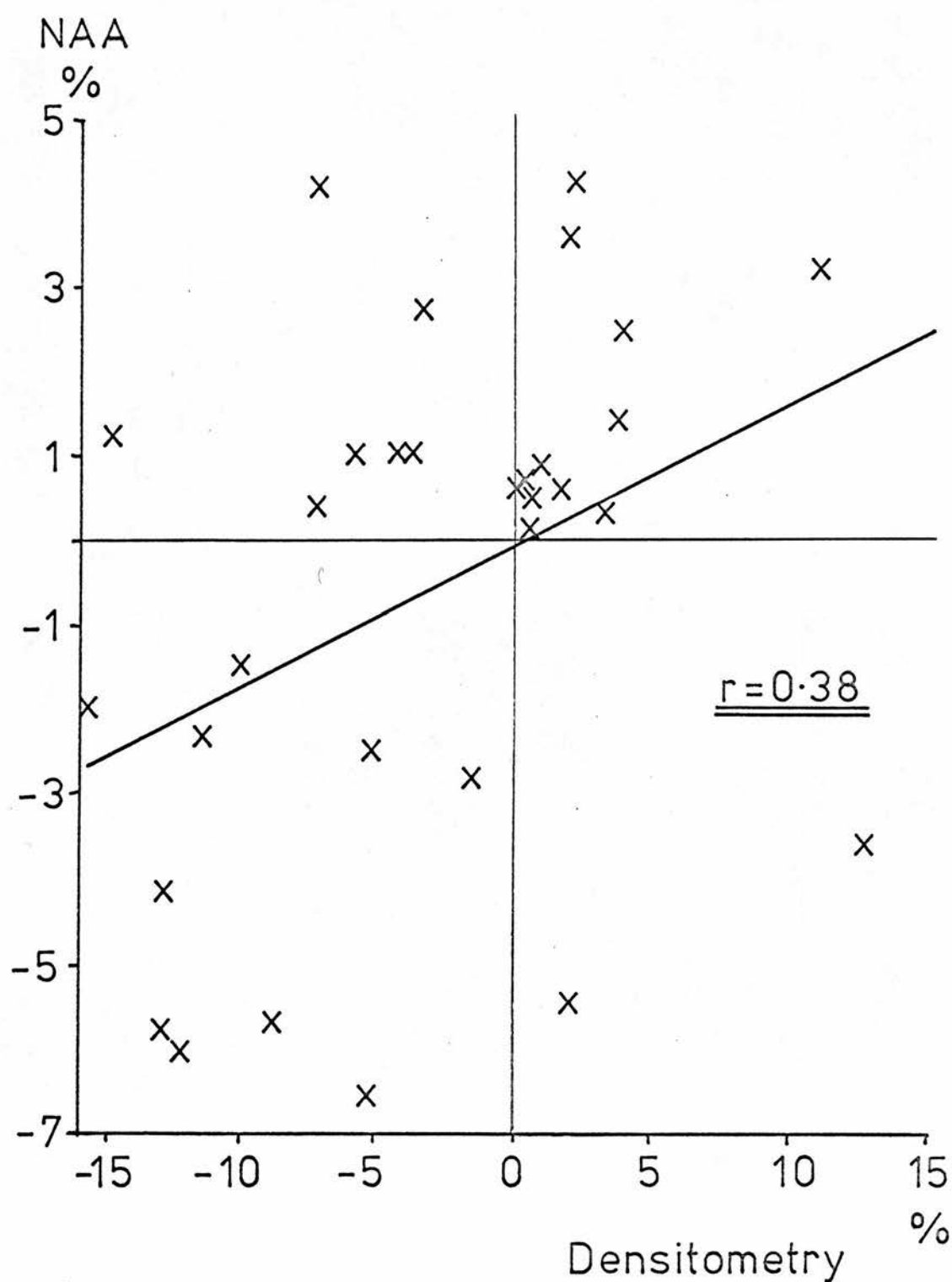


Figure 7.18

NAA changes v. Densit. changes
anticonvulsant patients



place. If this were true it may explain why there was no correlation between the various tests.

In the renal patients no correlation was found, over the first 8 months, where significant changes occurred, between activation analysis and metacarpal indices. Using all the results, correlations of $r = 0.16$ and $r = 0.19$ were found in the non-fistula and fistula arm respectively. When changes of greater than 50% were omitted, these correlations became $r = -0.06$ and $r = -0.17$.

As significant changes were recorded by activation analysis this poor correlation would tend to invalidate the technique of metacarpal indices in our hands.

CHAPTER 8.

CALCIUM MEASUREMENTS OF THE SPINE

While patient measurements were being performed on peripheral bone, work was in progress to design and build apparatus that would enable calcium measurements of the spine to be carried out. Calcium changes in the spine, particularly the lumbar region, are of great interest clinically, more so probably, than changes in peripheral bone. Technical difficulties, however, have dissuaded many people from attempting direct measurements on the spine. Instead, much work has been done to register changes in the spine by indirect methods such as whole body activation analysis or measurements of trabecular bone at peripheral sites.

The only direct measurements of the spine by activation analysis have been done at Toronto (McNeill et al 1973b) and Birmingham (Al-Hiti et al 1976a,b) and these have been discussed in Chapter 1. Of these two, only the method of Al-Hiti measured predominantly the spine, and the apparatus that was used, a cyclotron, made it an impractical method for most hospitals. Experiments were therefore performed with a view to devising a method for measuring changes of calcium in the lumbar region of the spine using ^{252}Cf , with an acceptable dose to the patient and with a sufficiently high degree of precision. Such a technique, if it were proved successful, could feasibly be installed in any hospital.

8.1 Anatomy of the Spine

The lumbar spine is a region of metabolically active bone, the spinal cancellous, or trabecular, bone having approximately four times the turnover rate of dense bone (Marshall et al 1973). In the lumbar vertebrae approximately 75% of the bone is trabecular, which is the highest proportion of any bone in the body. A very high proportion of this trabecular bone is contained in the bodies of the vertebrae, the load bearing section, and a symptom of excessive calcium loss is the appearance of compression fractures in the body of the vertebrae. Ideally then, any measurements of calcium changes in the spine should be designed to measure predominantly the bodies of the vertebrae in the spine.

There appears to be some slight disagreement in the literature concerning the position of the spine below the skin surface. Al-Hiti (1973a) stated in a graph that the approximate region of spine extended from 0.5 cm to 6 cm below the skin surface and quoted non-uniformity of measurement through the spine accordingly. In a feasibility study for activation measurements of the spine (Glaros 1975), non-uniformity values were given for the ranges 0 - 3 cm, 0 - 5 cm and 0 - 7 cm.

Both these studies, however, underestimated the depth of the spine, according to the results of a survey of a large group of patients (Brinkley and Master 1967). X-ray films of adult myelograms were measured for 117 males and 80 females, and the distances D_S , skin surface to inter-

spinous line, and D_B , interspinous line to posterior surface of vertebral body, were noted for all the vertebrae. The maximum, minimum and average values for the lower thoracic and lumbar spine are shown in Table 8.1. From this table it can be seen that the bodies of the vertebrae are situated at a much greater depth below the skin surface than was suggested by Al-Hiti or Glaros. Therefore, in the experiments that were performed with the ^{252}Cf sources, uniformities of activation and detection were measured in the range 5 cm to 9 cm.

TABLE 8.1

Depth of Spine below Skin Surface

	D_S			D_B			$D_S + D_B$
	Min	Max	Mean	Min	Max	Mean	Mean
T8	0.4	1.9	1.0	2.9	4.6	3.7	4.7
9	0.4	1.8	0.8	3.1	4.7	3.7	4.5
10	0.3	2.4	0.8	3.0	4.8	3.8	4.6
11	0.3	2.1	0.9	2.9	5.0	4.0	4.9
12	0.3	2.0	0.9	2.6	5.0	4.4	5.3
L1	0.4	2.0	1.0	3.6	5.7	4.7	5.7
2	0.4	1.9	1.1	4.0	6.2	5.0	6.1
3	0.6	2.7	1.3	4.0	6.2	5.2	6.5
4	0.8	3.3	1.7	4.2	5.7	5.2	6.9
5	1.0	3.4	2.0	3.8	5.7	4.7	6.7

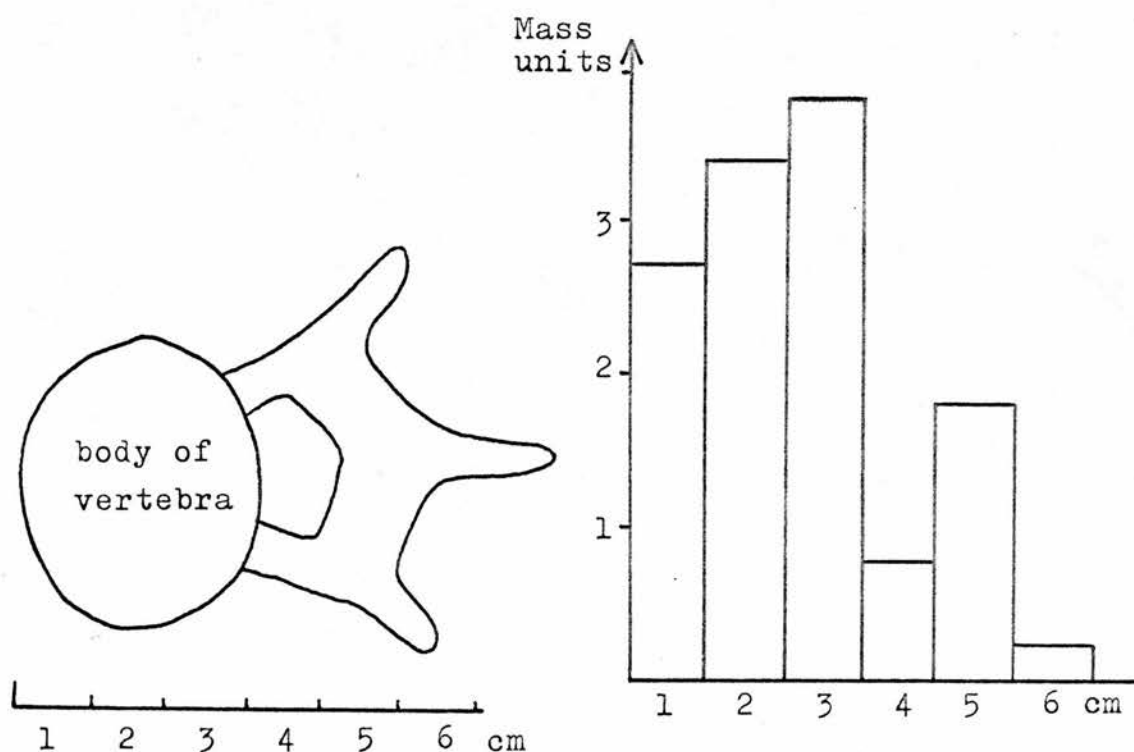
Another factor to consider was the distribution of calcium in the vertebral body. Although calcium changes

in the bodies of the vertebrae were the main concern, a proportion of the calcium counts measured would come from the spinous processes and arches. Counts from these regions would effectively increase the "background" counts, as far as vertebral body measurements were concerned, and reduce the chance of measuring any changes. Care had to be taken in the design of the method, not just to obtain the maximum number of ^{49}Ca counts or to obtain uniformity of measurement over the whole depth of the spine, but to reduce the counts from the spinous processes and arches and to increase the counts and uniformity in the region 5 cm to 9 cm deep.

An indication of the distribution of calcium in a vertebra is given in Figure 8.1. The histogram was

FIGURE 8.1

Distribution of Calcium in the Vertebra



obtained by taking four lumbar vertebrae and measuring their mass distributions, using Archimedes' principle, assuming that the calcium distribution was similar. The results showed that approximately 77% of the mass of a vertebra was in the body.

8.2 Detection of Induced Activity in the Spine

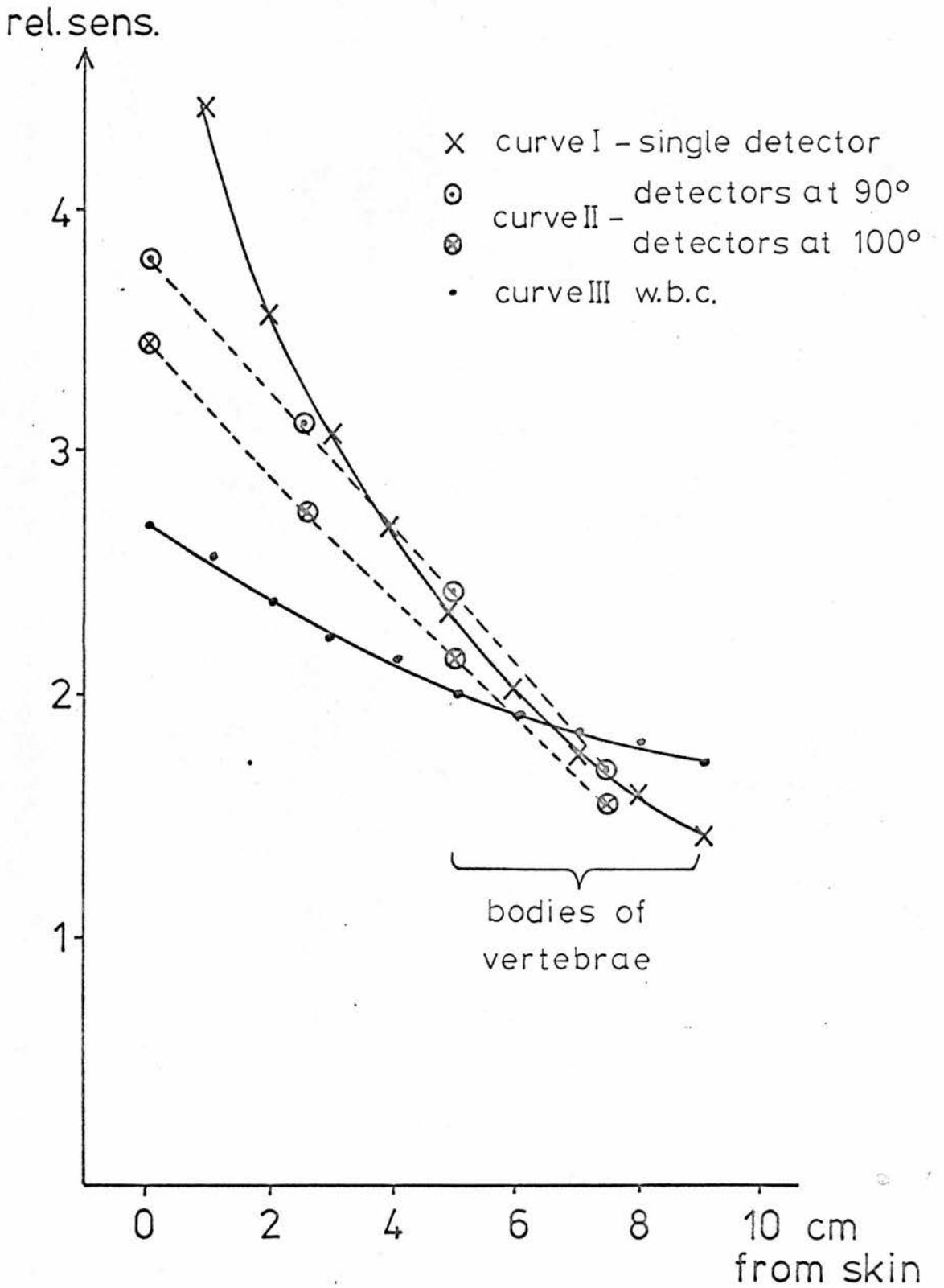
Because there are fewer possible variations in detection geometry, this was investigated first, so that the activation geometry could be chosen accordingly. There were three possible methods of measuring the induced activity and the sensitivity and uniformity of each of these were measured using a 20 cm long, 1 cm diameter tube of ^{24}Na in a water bath. As a section of the spine was to be measured, it was felt that an extended source would be more suitable than a point source.

Initially measurements were performed using the part body counters. In the first method a single 15 cm x 10 cm NaI detector was used without the central shield and positioned so that a patient's back could rest against the detector. The variation in sensitivity is shown in curve I in Figure 8.2, and the variations in the regions 1 cm to 5 cm and 5 cm to 9 cm were $\pm 30.2\%$ and $\pm 24.0\%$ respectively.

The second geometry considered was two 15 cm x 10 cm detectors used together at an angle of 90° and 100° with the crystals touching. The variation along the line bisecting the angle between the detectors (curves II, Fig. 8.2) was calculated from measurements of one detector and

Figure 8.2

Variation in counting sensitivity
at 2.75 MeV



it was assumed that the skin surface of a patient would be 8 cm from the point where the detectors touched. The sensitivity and uniformity, however, were little improvement on the first method, except over the first few centimetres.

The third and last counting geometry to be examined used the whole body counter available in the department. Four 15 cm x 10 cm detectors could be used, two above and two below, with the subject lying on a movable bed. The position of the detectors was adjusted to bring them as close as possible to the bed on which the patient would lie. The separation between the centres of the detectors was 20 cm in the horizontal direction between each pair above or below the patient and 41 cm in the vertical direction between the two pairs either side of the patient.

The variation in sensitivity with depth, using the whole body counter, is shown in curve III in Figure 8.2. It can be seen that the uniformity is a great improvement over that for the single detector, due to the bilateral counting geometry, the variations over the regions 1 cm to 5 cm and 5 cm to 9 cm being $\pm 11.5\%$ and $\pm 8.0\%$ respectively. Not only was the uniformity good but also the sensitivity, in the region of the bodies of the vertebrae, was approximately equal to that for the single crystal which would touch the patient's back.

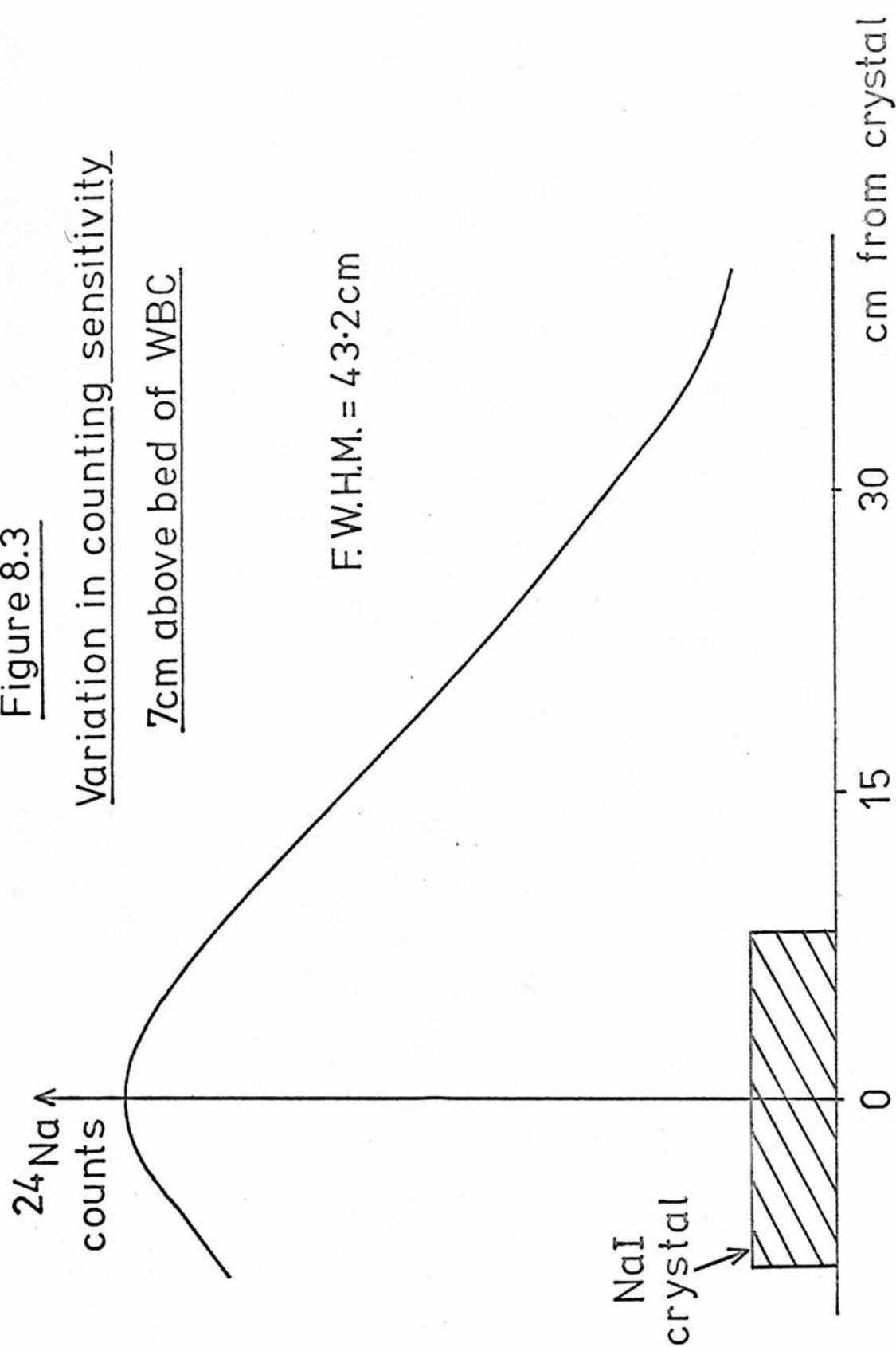
A further advantage of the whole body counter was the large F.W.H.M. in the direction perpendicular to the plane containing the detectors (Fig. 8.3). The F.W.H.M. was

Figure 8.3

Variation in counting sensitivity

7cm above bed of WBC

F.W.H.M. = 43.2 cm



43.2 cm at a distance 7 cm above the bed, compared with 23 cm at 7 cm from the face of one of the crystals of the part body counter. This would enable a larger section of the spine to be activated.

It was felt, also, that it would be easy to position a patient in a reproducible fashion fairly quickly using the bed of the whole body counter, and that he would be less likely to move or fidget if he were supine. For all these reasons it was decided to use the whole body counter for the detection of induced activity.

8.3 Activation of the Spine

The problem of choosing the best activation geometry was much greater than choosing the detection geometry, because there was a much larger number of variables from which to choose the optimum combinations. The properties of the ideal irradiation geometry can be summarised as follows:

- (A) High sensitivity of activation in the region of the bodies of the vertebrae (5 cm to 9 cm).
- (B) Low sensitivity of activation in the region of the spinous process and arches (0 cm to 5 cm).
- (C) Uniformity of activation through the region of interest (5 cm to 9 cm).
- (D) An activation profile along the spine that is compatible with the detection profile of the

whole body counter.

- (E) Low dose to the skin surface and radio-sensitive organs, especially the bone marrow.

The properties of the irradiation apparatus depend on the following variables. More often than not, each variable will affect more than one particular property of the irradiation geometry.

- (a) Source position.
- (b) Thickness and position of premoderator.
- (c) Quantity of reflector around the sources.
- (d) Presence of a thermal neutron absorber such as cadmium.
- (e) Whether the sources are stationary or moving.
- (f) Source strength.
- (g) Neutron energy.

An additional complication arises if it were decided to measure phosphorus as well as calcium. It was considered when designing the apparatus that the ability to measure phosphorus was not of prime importance but that it should be pursued, if possible, on the condition that it did not interfere with the calcium measurements.

The possibility of theoretically determining the thermal flux profile, for different values of the variables above, was investigated. Monte-Carlo techniques would have to be used (Raeside 1976, Carlson) but the time or facilities were not available to develop a mathematical model for the proposed activation apparatus. Other groups have

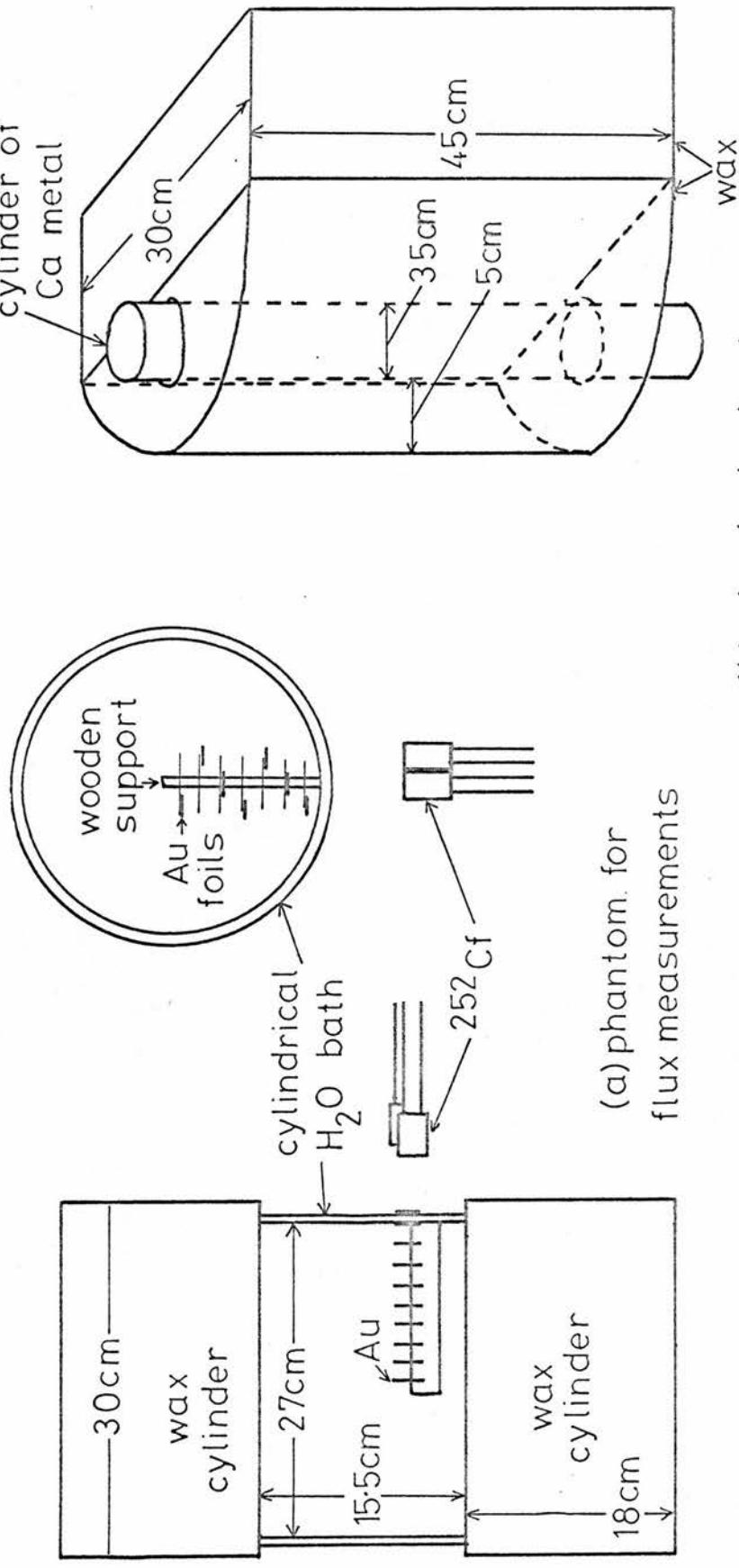
used Monte-Carlo techniques for neutrons (Jones and Auxier 1971a, Jones et al 1971, Krishnaswamy 1971a, 1971b, Nagarajin and Iger 1974) but the calculations were extremely complicated with just simple source/phantom arrangements. Available Monte-Carlo computer programmes were investigated (Hannan et al 1973, Frigerio et al 1973) but they could not have coped with the variations in irradiation geometry that were to be investigated. An experimental approach was therefore adopted.

The properties of a whole range of irradiation geometries were tested using the phantoms shown in Figure 8.4. The premoderator material, when used, consisted of sheets of perspex, and the thermal neutron absorber was a sheet of cadmium 1 mm thick. This thickness of cadmium may have caused slightly more reduction in sensitivity than was necessary, as a sheet 0.4 mm thick was used for a similar purpose in Birmingham (Vartsky and Thomas 1976). The strength of each source for these experiments was 31 mCi and both sources were used together, adjacent to one another.

8.4 Variation of Thermal Neutron Uniformity with Depth.

The variation in thermal neutron fluence with depth was the first thing to be investigated in a range of irradiation geometries listed in Table 8.2. Measurements were made every centimetre using gold foils which were staggered to avoid excess absorption in the foils nearest the sources. The curves of the variation in thermal fluence with depth

Figure 8.4
Phantoms for spine studies



are shown in Figures 8.5a and 8.5b, the individual data points, which fit the curves very well, being omitted for clarity. The results obtained from the curves were the variation in the region 5 cm to 9 cm, the relative thermal flux at 7 cm and the approximate position of the peak below the "skin" surface (Table 8.2).

In all cases where measurements were performed with and without reflector, the presence of a reflector was found to decrease the uniformity at depth, to move the peak thermal flux value nearer the surface and to increase the flux at 7 cm. When a thickness of premoderator, which was less than the source to skin distance, was used, the premoderator was best left against the source to improve the uniformity at depth and the position of the peak. This was to be expected because when the premoderating material was next to the skin its effect as a reflector was greater than when it was adjacent to the sources. The amount of premoderator obviously had an effect on the shape of the curve and, in general, the greater the thickness of premoderator, the worse the uniformity of thermal fluence at depth. The presence of the sheet of cadmium shifted the thermal peak away from the surface but did not dramatically improve the thermal fluence uniformity at depth.

From the curves in Figure 8.5 and the results in Table 8.2, it can be seen that geometry 2 gives the best thermal neutron depth profile. Not only was the uniformity good in the region 5 cm to 9 cm, but the thermal fluence was relatively low over other regions of the vertebrae nearer

TABLE 8.2

Variation in Thermal Flux for Different Irradiation Geometries

Geometry	Premoderator (cm)	S.S.D. (cm)	Reflector	Posn. of Peak (cm)	Relative Fluence at 7 cm	Variation 5cm-9cm (%)
1	0	0	No	3.8	2.77	± 33
2	0	6	No	4.0	0.92	± 22
3	6	6	No	No peak	0.90	± 49
4	6	6	Yes	No peak	1	± 54
5	2.1 to skin	6	No	2.3	1.04	± 33
6	2.1 to source	6	No	2.6	1.04	± 31
7	2.1 to source	6	Yes	1.4	1.40	± 40
8	3.2 to skin	6	No	1.5	1.02	± 33
9	2.1 to source	12	Yes	1.5	0.75	± 32
10	2.1 + Cd	2.2	Yes	2.3	2.08	± 37
11	2.1 + Cd	2.2	No	2.7	1.71	± 33
12	3.2 + Cd	3.3	Yes	2.3	1.56	± 39
13	2.1 to source + Cd	6	Yes	2.6	1.23	± 37
14	As 7 but bilateral irradiation through 23 cm			1.4	0.78	± 29

Figure 8.5a

Variation in thermal flux with depth for
geometries 1 to 9

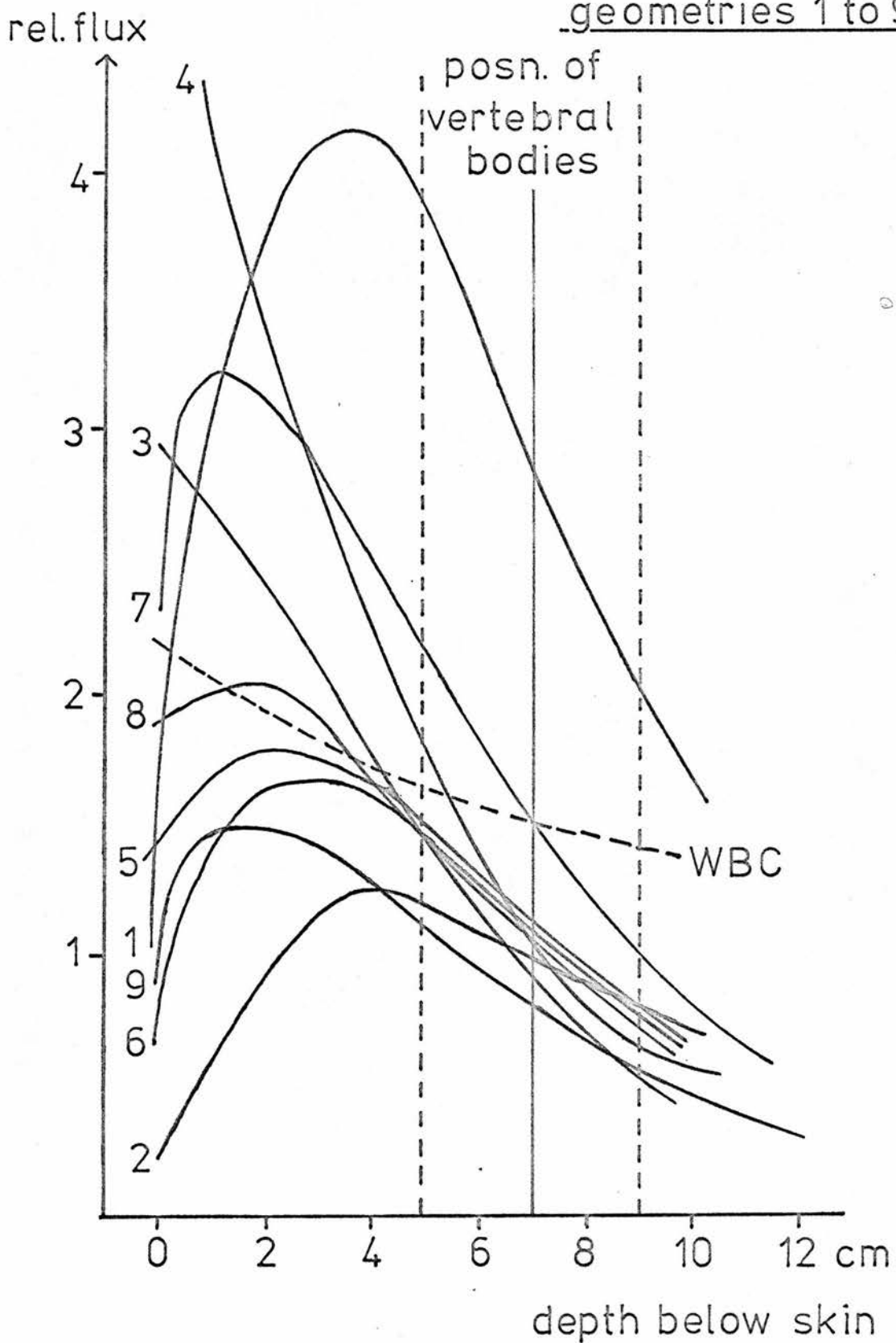
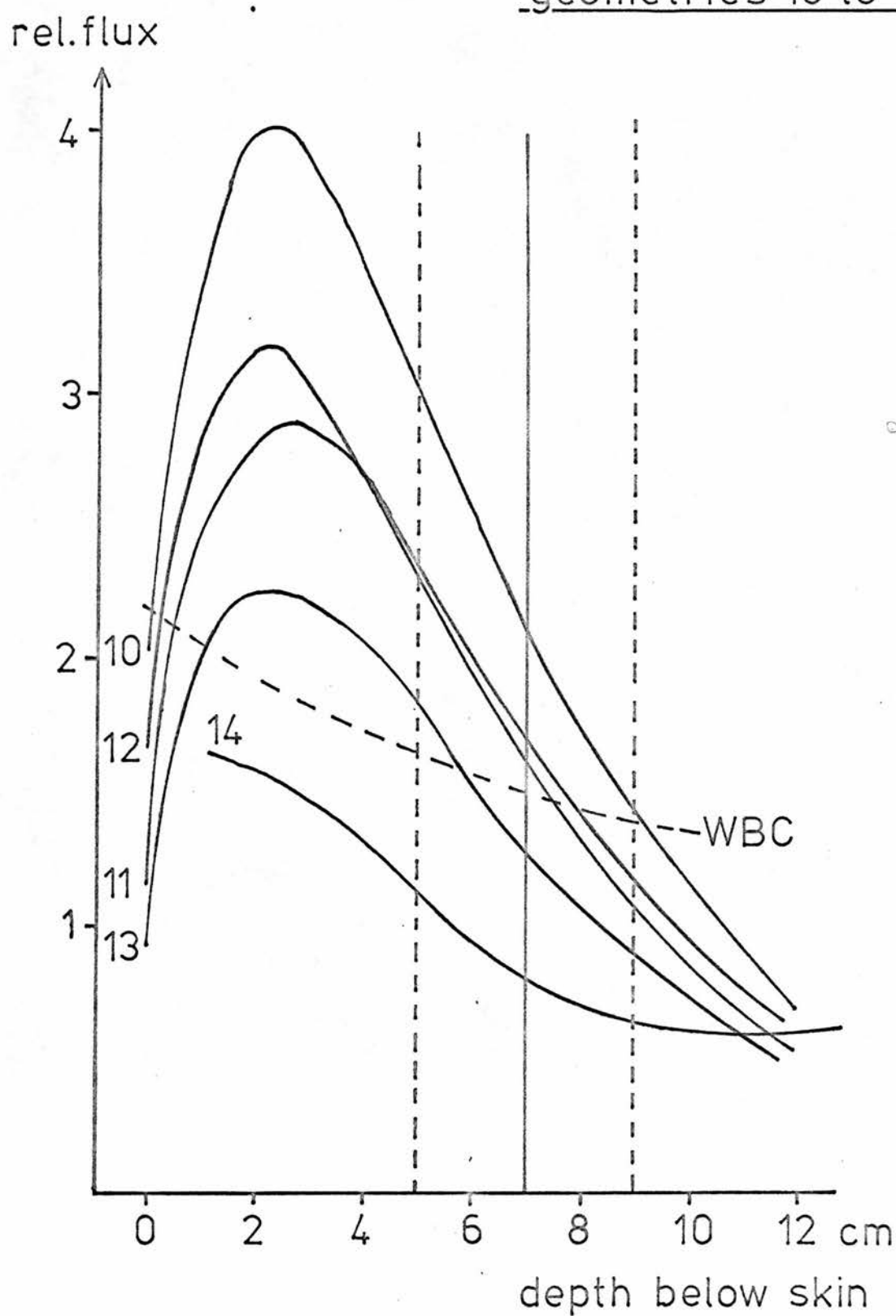


Figure 8.5b

Variation in thermal flux with depth for
geometries 10 to 14



the skin surface.

8.5 Dose Distribution

The neutron and gamma doses were measured in a range of irradiation geometries using nuclear emulsions supplied and measured by the National Radiological Protection Board. In addition to measuring the maximum dose at the skin surface and at 7.5 cm deep, measurements were made along the surface of the phantom to obtain the F.W.H.M. of the dose distribution. The dose distribution was also measured at 7.5 cm below the surface, in the direction parallel to the spine, using a fission chamber. At this depth the majority of the dose would come from fast neutrons, so the fission chamber would give an adequate estimation of the F.W.H.M. of the dose distribution.

The results of the dose measurements are given in Table 8.3 which also includes the peak doses that would be obtained if the two sources were separated by 20 cm. Such a separation would reduce the peak dose by an amount which depended on the F.W.H.M. of the dose profile, as is shown in Figure 8.6. A reduction could also be obtained if the two sources were placed together and scanned along a section of the spine. This reduction is also shown in Figure 8.6.

It can be seen in Table 8.3 that the presence of reflecting material reduced the skin dose (geometries 2, 15 and 3, 4), which was not expected. This could have been due to the confined space in the activation chamber

TABLE 8.3

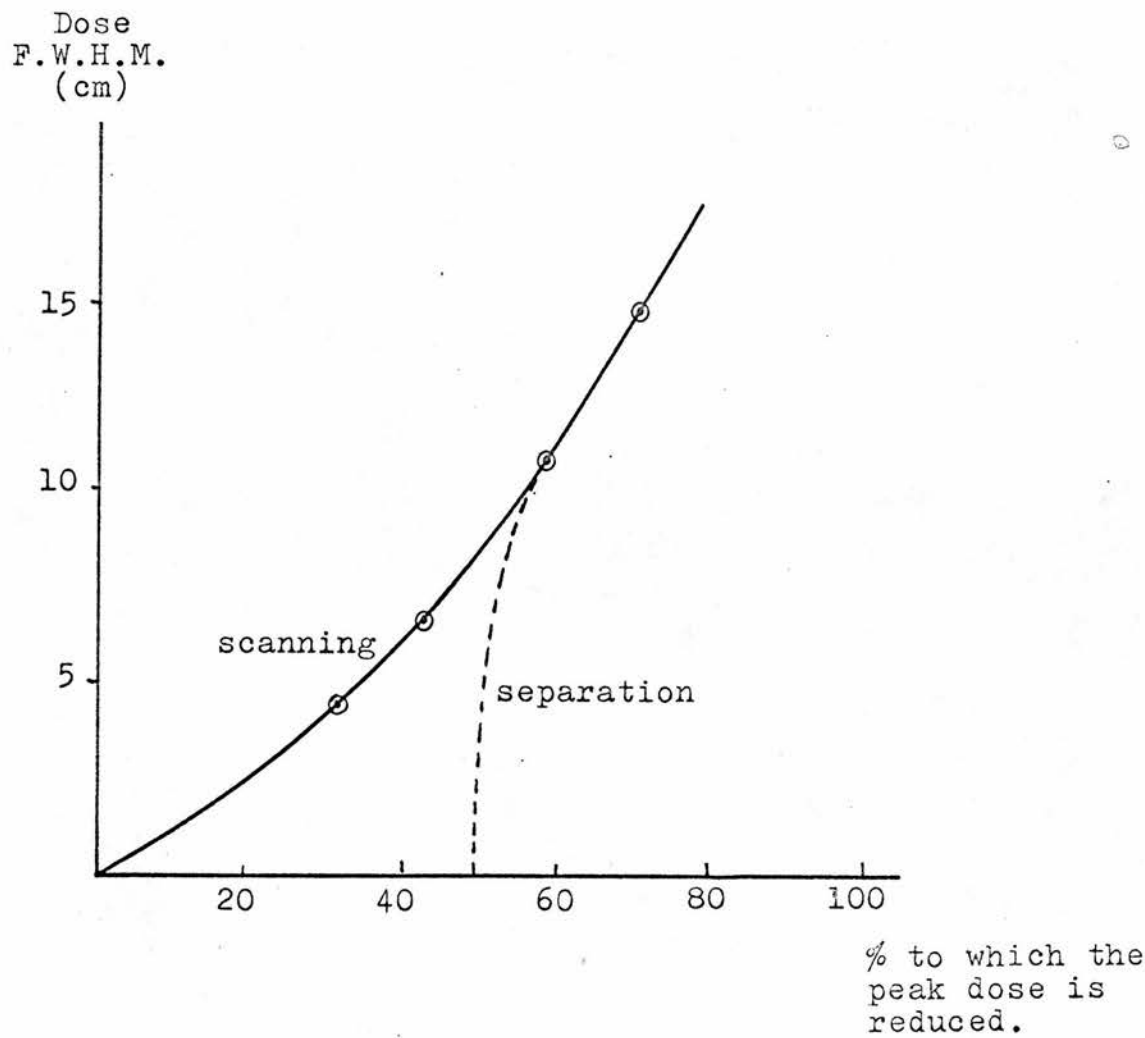
62 mCi ^{252}Cf Dose for Difference Irradiation Geometries

<u>Geometry</u>	<u>Premod.</u> (cm)	<u>S.S.D.</u> (cm)	<u>Reflector</u>	<u>Peak Dose</u> (rem.min ⁻¹)		<u>F.W.H.M.</u> (cm)		<u>Peak Dose</u> 20 cm separation (rem.min ⁻¹)	
				skin	bone	skin	bone	skin	bone
2	0	6	No	1.377	0.110	8.4	12.1	0.689	0.069
15	0	6	Yes	0.993	0.12	14.6	12.8	0.680	0.078
3	6	6	No	0.584	0.075				
4	6	6	Yes	0.489	0.075	10.6	11.2	0.276	0.045
16	3.2	6	Yes	0.803	0.102	10.2	12.8	0.437	0.066
12	3.2	3.2	Yes	1.606	0.110	6.6		0.670	
10	2.2	2.2	Yes	3.570	0.150	4.5		1.060	

and the fact that the thick shielding wall was about 1 m or less from the sources, hence reflecting some fast neutrons back to the phantom. The presence of the block of wax reflector probably eliminated this contribution to the dose.

FIGURE 8.6

Reduction of Peak Dose Obtained by Separation
or Scanning over a 20 cm Region



8.6 Sensitivity of Calcium Activation

The sensitivity cannot be accurately obtained from the thermal flux variations with depth (Table 8.2 column 6), because only one dimension was considered whereas the problem was two dimensional. In addition it must be remembered that two figures need to be stated for the spine sensitivity; the total number of ^{49}Ca counts and also the approximate number of counts from the bodies of the vertebrae.

For this reason both the calcium phantom (Fig. 8.4b) and a cadaver torso were irradiated in different irradiation geometries. The torso was obtained from the Department of Anatomy and had been stored in formalin. It was a fairly recent male specimen of late middle age, height approximately 5 ft 8 in, so any calcium losses due to osteoporosis etc. while alive, or leaching after death, would be minimal. The limbs had been severed from the torso at mid-thigh and at the top of the arms rather than disarticulated.

The values of the relative and absolute sensitivities are shown in Table 8.4. Estimations of the absolute calcium counts from the bodies of the vertebrae were obtained using the additional information given previously in Figures 8.1 and 8.2. The irradiation and counting times for the cadaver torso were 10 min and 1000 s respectively, the latter being performed on the whole body counter. It can be seen that though geometries 4 and 7 had over twice as many ^{49}Ca counts as geometry 2, the numbers from the

TABLE 8.4

Sensitivity of Activation and Detection for Different
Irradiation Geometries.

<u>Geometry</u>	<u>Premod. (cm)</u>	<u>S.S.D. (cm)</u>	<u>Reflector</u>	<u>Relative</u>		<u>Relative Sensitivity</u>		<u>Cadaver</u>		<u>⁴⁹Ca Counts</u>
				<u>thermal flux at 7 cm</u>		<u>Body Phantom</u>	<u>Cadaver</u>	<u>Total</u>		<u>Approx. counts from bodies of vertebrae</u>
2	0	6	No	0.92		0.91	0.49	1218		1130
4	6	6	Yes	1.00		1.00	1.00	2493		1250
7	2.1	6	Yes	1.40		1.40	1.03	2573		1750
10	2.1 + Cd	2.2	Yes	2.08		1.72				2140
11	2.1 + Cd	2.2	No	1.71		1.39				1730

bodies of the vertebrae were not much larger. Thus although geometry 2 had the lower number of counts, most of these came from the vertebrae bodies.

8.7 Phantom Reproducibility

As this was by far the most time-consuming of all measurements, repeated tests were only performed using geometries 2 and 4, being examples of good and bad depth uniformity respectively.

- (i) Geometry 4; 6 repeated measurements were performed using the spine body phantom:

$$\text{Mean} = 3314$$

$$\text{C.V.}_T = 2.02\%$$

the number of counts is meaningless; the important value is C.V._m , coefficient of variation due to movement:

$$\sigma_m = 34.43$$

$$\text{C.V.}_m = 1.04\%$$

- (ii) Geometry 2; 6 repeated measurements were performed using the spine body phantom:

$$\text{Mean} = 3439$$

$$\text{C.V.}_T = 1.86\%$$

$$\sigma_m = 25.3$$

$$\text{C.V.}_m = 0.74\%$$

As would be expected, the reproducibility of geometry 2 was superior but not by a great deal.

- (iii) Geometry 2; 9 repeated measurements were made with the cadaver torso:

$$\begin{aligned} \text{Mean} &= 1189.7 & \sigma_T &= 41.2 & \text{C.V.}_T &= 3.5\% \\ & & \sigma_S &= 34.5 & \text{C.V.}_S &= 2.9\% \\ & & \sigma_m &= 22.6 & \text{C.V.}_m &= 1.9\% \end{aligned}$$

However one of the 9 readings was significantly different from the rest and it would have been statistically valid to discard it using Chauvenet's criterion (Geigy 5th edition) the value being different from the mean by 5.3σ . If it were discarded the value for C.V._T would be reduced to 1.5%.

8.8 Source Strength

The minimum source strength required to obtain adequate counting statistics over a reasonable time scale had to be determined. This required the precision of the measurement of calcium in the bodies of the vertebrae to be estimated. Now this is not to say that any attempt was made to state the number of ^{49}Ca counts from the bodies of the vertebrae, but that the statistical error of the total counts had to reflect the error in the measured counts from the ^{49}Ca at depth. Such a calculation of the precision enabled a more realistic determination of the minimum detectable change of calcium in the spine and hence the source strength required.

$$\therefore C.V._S = \frac{\sqrt{\text{Total } ^{49}\text{Ca counts} + \text{bgd}}}{^{49}\text{Ca counts from bodies of vertebrae}}$$

Assuming $C.V._m = 2\%$ (from cadaver tests)

$$\therefore C.V._T = \sqrt{(C.V._S)^2 + (C.V._m)^2}$$

The values used in the calculation of $C.V._S$ are obtained from Table 8.4 and extrapolations of these figures for higher source strengths. The results are given in Table 8.5, and graphs of the estimated precision versus dose for different source strengths and irradiation geometries are shown in Figure 8.7.

TABLE 8.5						
<u>Estimated Precision of Calcium in the Vertebral Bodies with Different Source Activities</u>						
<u>Geo- metry</u>	<u>60 mCi</u>		<u>120 mCi</u>		<u>180 mCi</u>	
	<u>σ_T</u>	<u>C.V._T</u>	<u>σ_T</u>	<u>C.V._T</u>	<u>σ_T</u>	<u>C.V._T</u>
4	70.56	5.7%	122.1	4.9%	172.8	4.6%
2	42.56	3.8%	69.35	3.1%	94.8	2.8%
7	72.26	4.1%	125.5	3.6%	177.6	3.4%

Because the precision ($C.V._T$) is expressed as a percentage of the approximate counts in the body of the vertebra, it will not tend to 2% at very large activities. It can be seen that, with 3 times the present activity, i.e. approximately 180 mCi, a precision of around 3% could be maintained over a several year period.

Figure 8.7a

Estimated precision versus dose

geometry 4:

(x,y) x \equiv activity (rel.)

y \equiv no. of irradiations

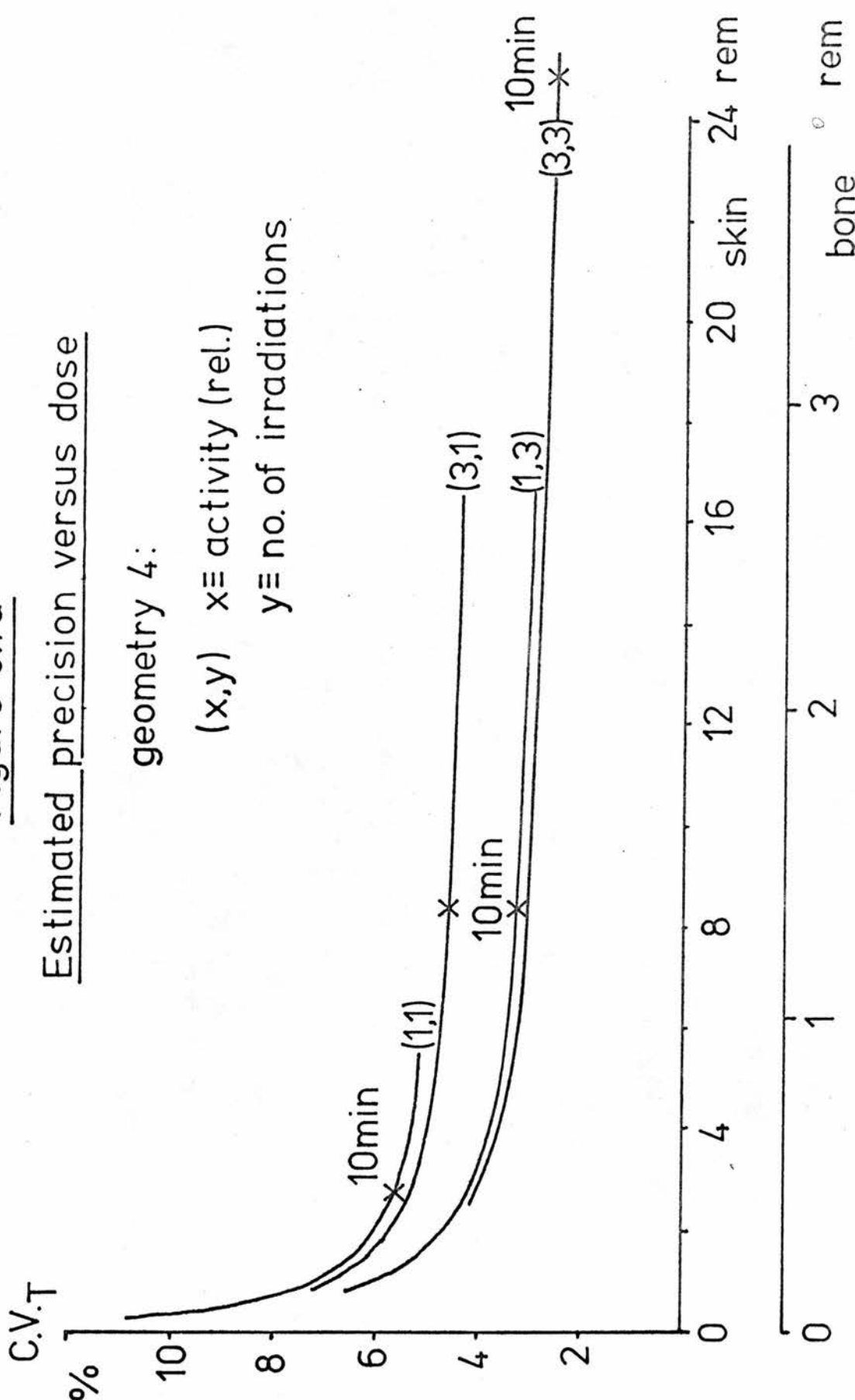


Figure 8.7b

geometry 7:

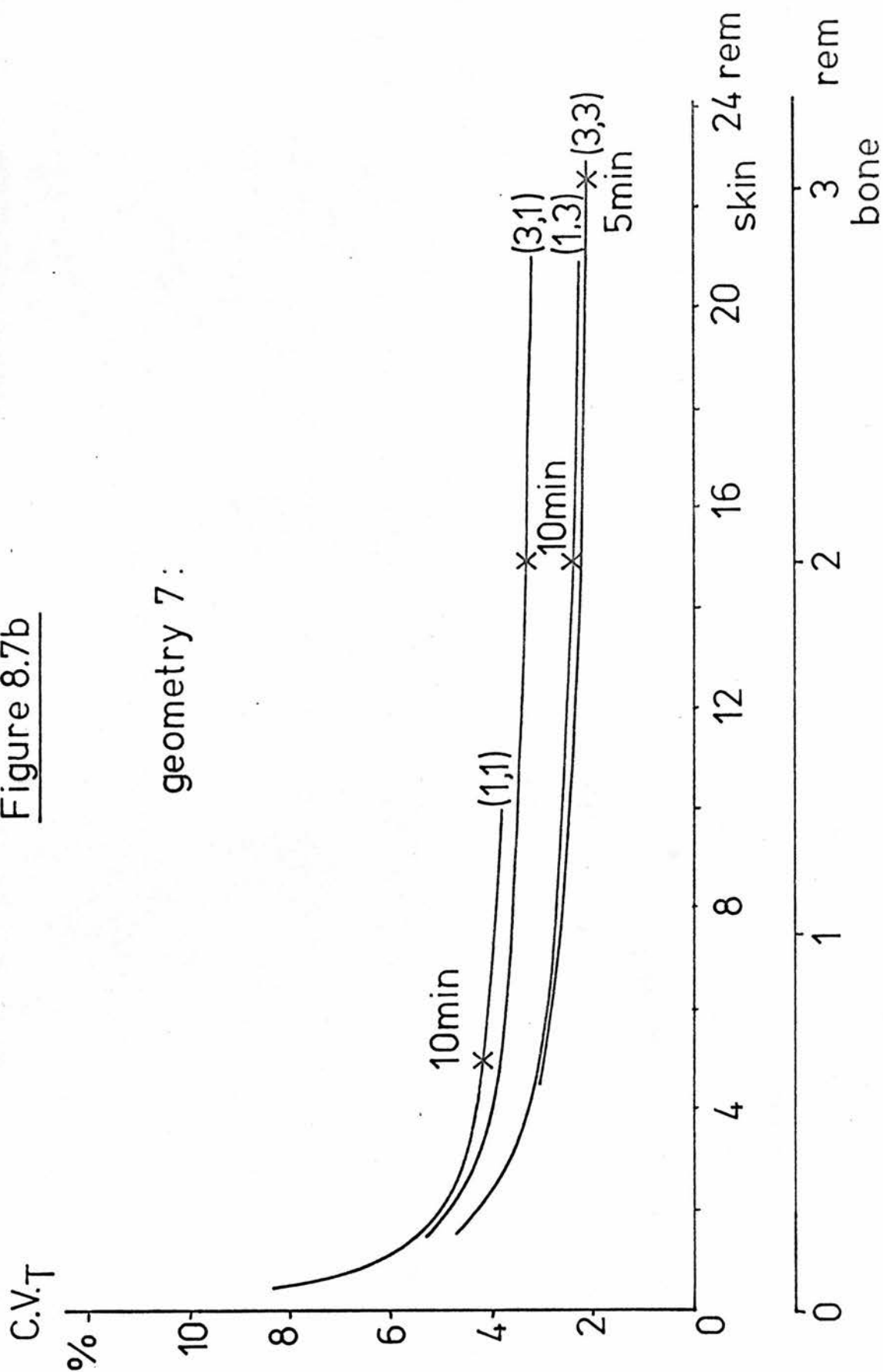
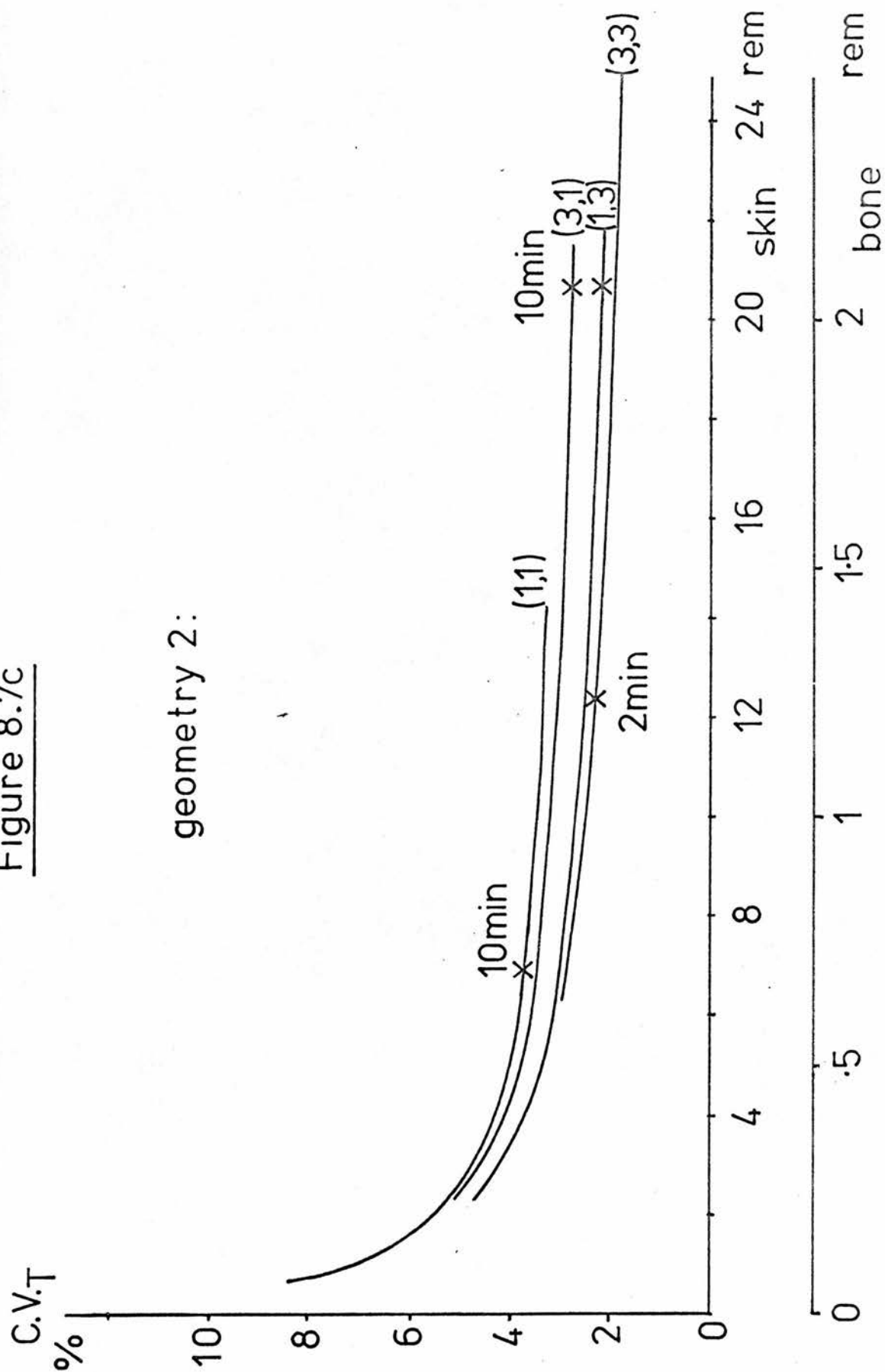


Figure 8.7c

geometry 2:



8.9 Optimum Irradiation Geometry

From the experiments performed, two irradiation geometries were considered suitable for spine measurements. The first, and possibly the best, irradiation geometry was No.2 where the S.S.D. was 6 cm and no reflector or premoderator was used. This gave the best uniformity of activation with depth and the lowest activation of the spinous process and arches of the vertebrae. The ^{252}Cf spectrum was not moderated in geometry 2 so it gave the best chance of detecting phosphorus in the spine. Also, the lack of reflector and premoderator gave a narrow dose F.W.H.M. at the skin surface. This meant that, by separating or scanning the sources over 20 cm, the peak skin dose could be reduced to an acceptable level.

Separating the sources by 20 cm changed the F.W.H.M. of the activation profile along the spine at 7 cm depth. The value was increased from 20.1 cm to 36 cm, if the sources were separated, and from 20.1 cm to 25.0 cm, if the sources scanned 20 cm. This did not unduly affect the efficiency of detection because the F.W.H.M. of the detection profile was 43 cm. Another advantage of viewing a long section of the spine was that sampling errors from too restricted a field were reduced.

Dose values for spine measurements using two 100 mCi sources are given in Table 8.6, and the variations in measurement sensitivity along the spine and with depth are shown in Figures 8.8 and 8.9.

It must be noted that the effect of either scanning a

TABLE 8.6

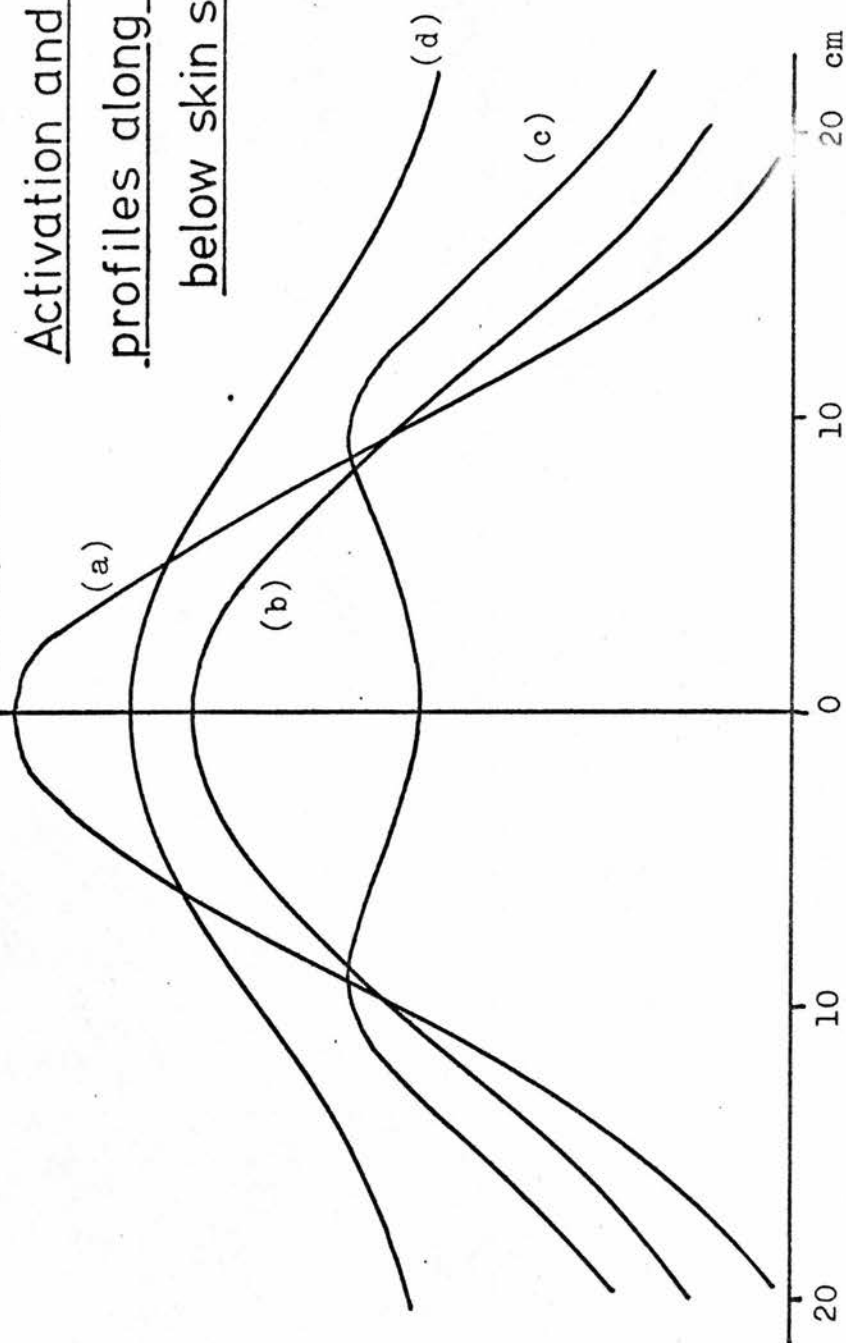
Dose to Spine for Optimum Irradiation Geometries

	<u>Geometry 2</u>		<u>Geometry 13</u>	
	6cm S.S.D. No Reflector or Premoderator		6cm S.S.D., Reflector., 2cm Premoderator next to sources, Cd Absorber	
	<u>300 s irradiation</u>		<u>400s irradiation</u>	
<u>Skin Dose</u>				
Peak dose, stationary sources	20.5 rem		18.0 rem	
F.W.H.M., stationary sources	8.4 cm		10.0 cm	
Peak dose, 20 cm scan	10.0 rem		9.9 rem	
F.W.H.M., 20 cm scan	22.1 cm		24.0 cm	
<u>Bone Dose</u>				
Peak dose, stationary sources	1.7 rem		2.2 rem	
F.W.H.M., stationary sources	12.6 cm		12.6 cm	
Peak dose, 20 cm scan	1.0		1.3 rem	
F.W.H.M., 20 cm scan	22.1 cm		22.1 cm	
Integrated dose along spine	21.3 rem.cm		28.4 rem.cm	
Dose averaged over 50cm	0.43 rem		0.57 rem	

^{24}Na counts for d \uparrow Thermal flux
for a, b and c

Figure 8.8

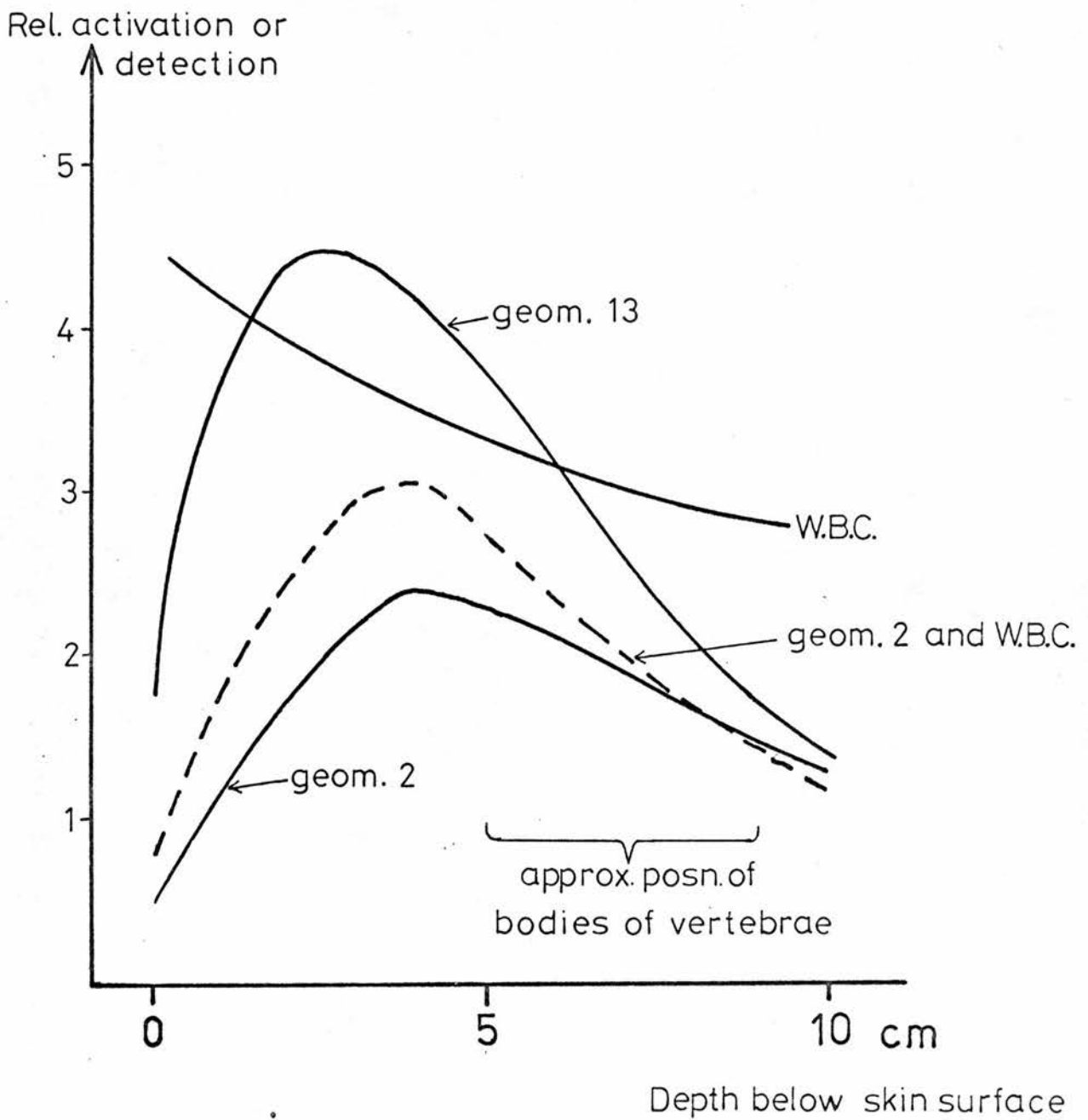
Activation and detection
profiles along spine 7cm
below skin surface



- (a) activation profile with sources in fixed position. F.W.H.M.=20.1cm
 (b) " " scanning 20cm. F.W.H.M.=25.0cm
 (c) " " separated by 20cm. F.W.H.M.=36.0cm
 (d) detection profile with whole body counter. F.W.H.M.=43.0cm

Figure 8.9

Variation in activation and detection with
depth for optimum geometries



20 cm region, or separating the sources by 20 cm, was essentially the same. If the value of 20 cm were to be increased then scanning would be superior.

The second irradiation geometry which was thought to be of use for spine measurements used a combination of reflector, premoderator and Cd sheet (Table 8.6 and Fig. 8.9). The uniformity of activation was not as good as for the first geometry, but its possible advantage was that the sensitivity of activation was greater and so may be of particular use for patients of small stature.

8.10 Design of Patient Irradiation Apparatus

An old dental chair was modified for patient irradiation. The back was removed and replaced by a back rest in two sections (Figs. 8.10a,b and 8.11a,b). The lower section contained a thin perspex window through which the lumbar spine could be viewed. The complete dental chair could be tilted back so that the lower back rest was at an angle of about 30° to the vertical. The upper section of the back rest could be tilted, pushing the patient's shoulders forward. This had the effect of eliminating any lordosis so that the lower thoracic and lumbar section of the spine touched the perspex window. With the chair tilted back, the patient's own weight held his back against the window and prevented any movement.

Attached to the lower back rest were various devices for the ^{252}Cf sources. The polyethylene source delivery tubes were inserted into two long perspex tubes, attached

Figure 8.10a

Spine irradiation apparatus

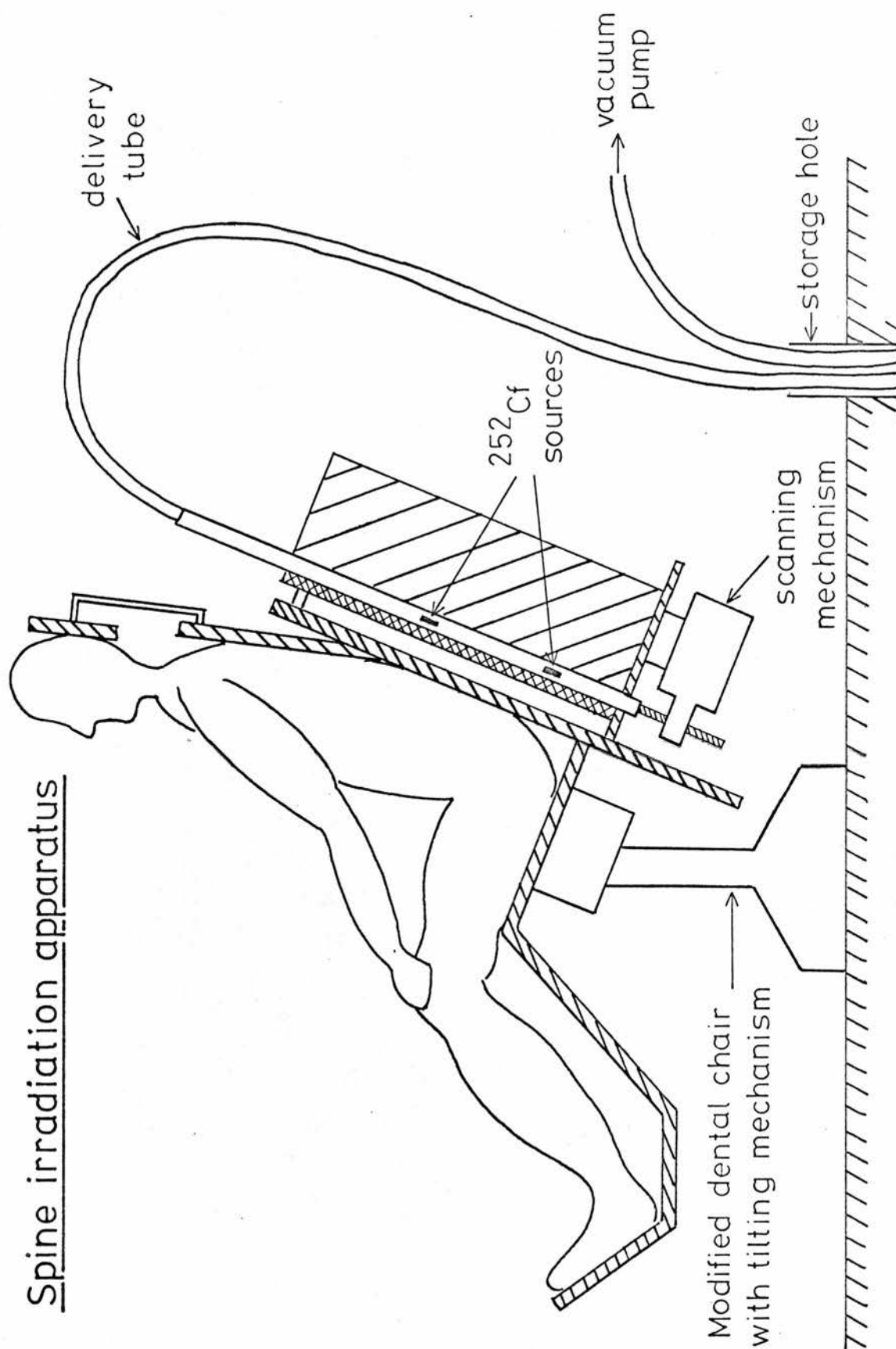


Figure 8.10b

Close-up of irradiation
assembly

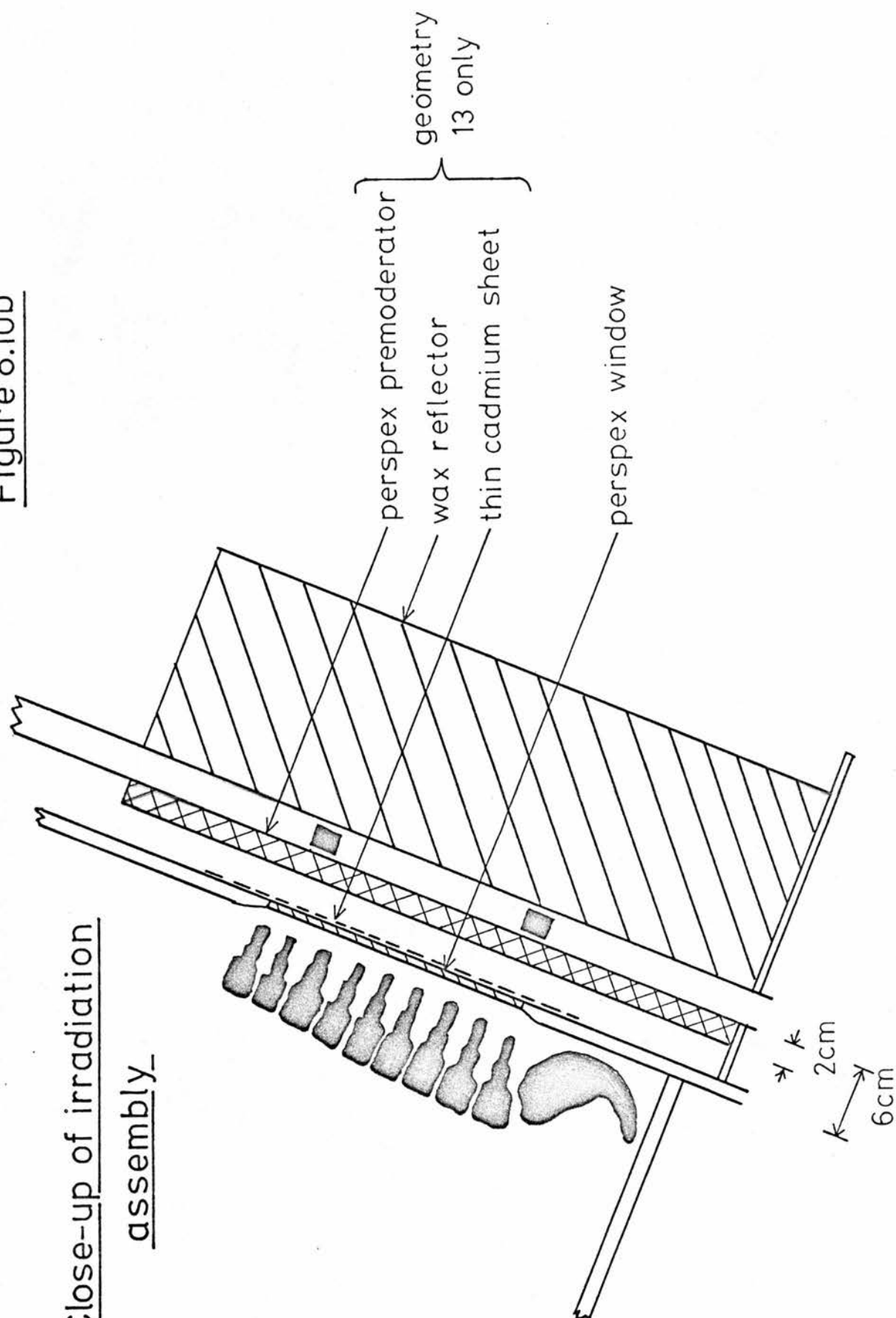
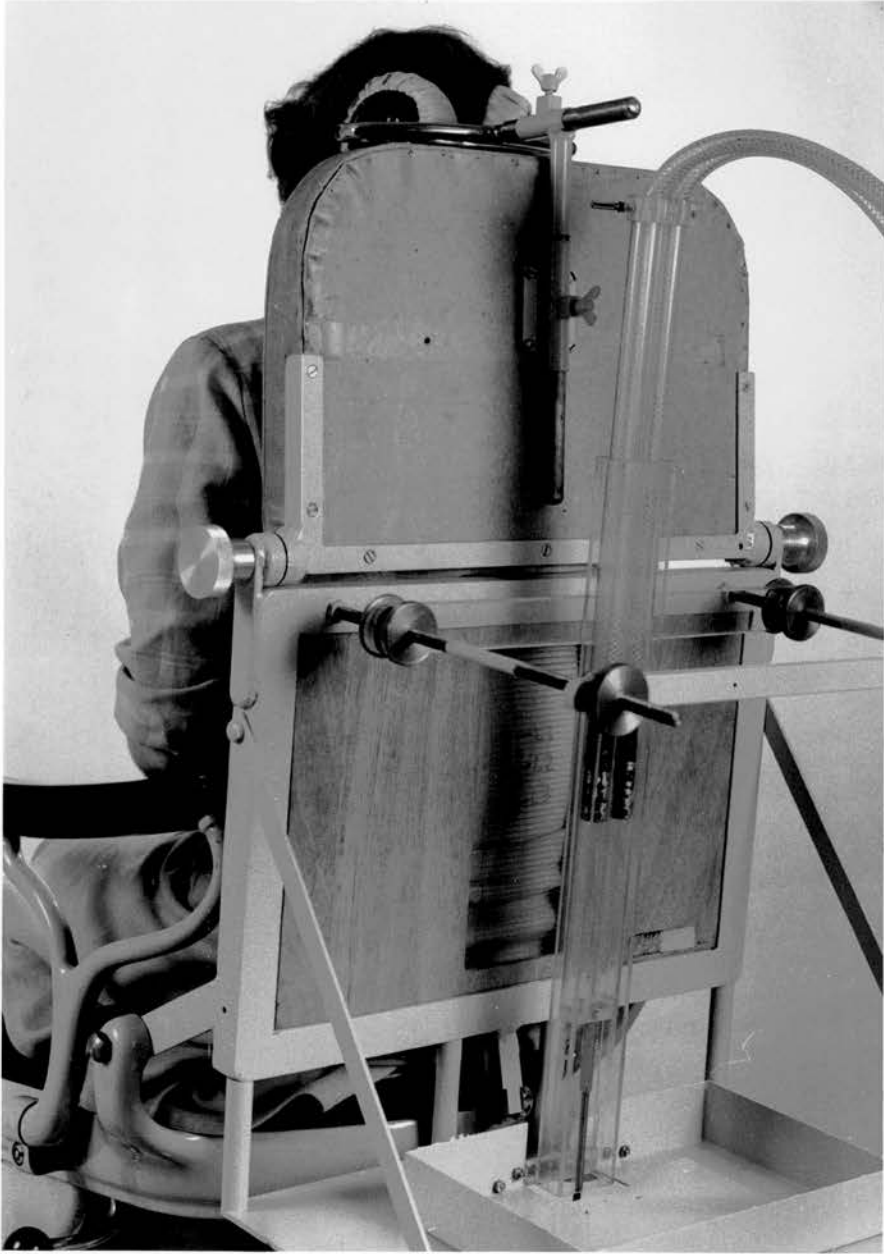


FIGURE 8.11a



Patient in spine irradiation apparatus with
wax reflector in position.

FIGURE 8.11b



Spine irradiation apparatus from the rear.
The position of the lumbar vertebrae can
be seen against the perspex window.

to one another, which could be moved up and down inside two supporting square perspex tubes. The position of the source delivery tubes could be fixed in the perspex tubes using a brass screw so that the metal end pieces, where the sources would be, could be positioned anywhere along the perspex tubes. The lower ends of these tubes were not air-tight to ensure adequate air flow for the pneumatic delivery system. The distance of the perspex tubes containing the sources away from the lower back rest could be adjusted in the range 3 cm to 15 cm.

The tubes containing the sources could be moved in the direction parallel to the spine using the electric motor at the base and a screwed rod attached to the perspex tubes. This was included in the design of the apparatus in case it was ever required to irradiate a longer section of the spine. The region for scanning could be defined using microswitches, and a tachometer connected to the motor ensured a constant scanning speed.

The plate at the base of the lower back rest was to support the wax reflector whenever it was used. A channel was cut out of the wax reflector so that it fitted round the rectangular source tube.

The back rests and motor could be folded forward and the foot support removed to make the chair small enough to fit into the activation chamber. The chair was mounted on a plate with wheels for ease of movement in and out of the activation room. Once in position, jacks in each corner of the plate could be screwed down to lift the wheels from the floor and immobilize the chair.

The electronics for driving the scanning mechanism on the chair were obtained from an old Nuclear Enterprises scanner which was being scrapped. Some modifications and rewiring were necessary, but eventually a unit was built which could move the sources back and forth manually or automatically at any set speed.

8.11 Spine Pilot Study

To evaluate the technique for measuring the spine, a small pilot study was performed on a group of ten volunteer patients using two 100 mCi ^{252}Cf sources. From this study a figure for the precision of calcium determination, the possibility of phosphorus measurement and the most suitable irradiation programme for patient studies, was determined.

Using the modified dental chair apparatus, a section of the spine was irradiated for 100s. The sources were positioned 20 cm apart, the centre of the separation distance being in line with the iliac crest. No reflector or premoderator was used and the centres of the sources were 6 cm from the skin surface. At the end of irradiation, the patient was measured using the whole body counter with the crystals as close to the patient as possible. The delay time varied from just over 1 min to over 3 min, the most common being 1 min 30 s to 1 min 45 s. The patient was counted for 3 x 400 s with the iliac crest at the centre of measurement. The full 1200 s were used to measure the calcium peak whereas only the first 400 s were used for phosphorus determination. The procedure was

repeated three times on all but one of the patients, who only had two measurements, there being a gap of at least one hour between the irradiations. For each patient, the measurements were all performed on the same day.

The calcium counts were determined using simultaneous equations, and the phosphorus counts by subtracting the second set of 400 s counts from the first. The results of the calcium measurements are shown in Table 8.7a. It can be seen that for this dose, a calcium count of about 1200 was obtained with a C.V. due to movement of about 1%. This gave an overall C.V. of 3.4%. Some of these patients had Paget's disease so the mean calcium counts may have been a slight overestimation.

It was found that the method was not suitable for clinical measurements of phosphorus in the spine. Although some of the patient spectra had a fairly large phosphorus peak, five out of the ten had a very small peak ($C.V._S > 10\%$). For further details see Appendix IV.

The apparatus for measuring the spine was developed mainly to investigate osteoporosis. As this is a disease in which the calcium loss occurs very slowly, it was decided to monitor each patient in the proposed study for about 18 to 20 months. Careful consideration had to be given to determine the optimum irradiation programme for the annual dose of 20 rem to the skin and 2.6 rem to the bone, for which permission was given by the M.R.C. and the local ethics committee.

Unlike the patient studies which have been completed,

TABLE 8.7a

Results of Spine Pilot Study

Patient	T irradi.	T delay	C.V. _T	C.V. _m	Mean Ca
C.R.	1m40s	1m40s	1.70	-3.76	822.4
A.H.	1m40s	1m30s	3.54	1.94	1534.2
L.G.	1m40s	1m15s	0.73	-2.44	1814.5
A.B.	1m40s	1m45s	4.33	1.66	847.4
I.S.	1m40s	1m15s	2.31	-3.40	824.1
J.G.	1m40s	1m10s	3.34	0.95	1223.3
J.M.	1m40s	1m10s	1.45	-2.81	1371.8
I.P.	1m40s	1m45s	4.73	3.29	1116.7
J.S.	2m	3m15s	7.66	6.99	1271.2
A.M.	2m	1m15s	8.38	7.69	1173.5

Mean Ca = 1199.7 ± 323.21

Mean C.V._m = 1.01% ± 4.16 (S.D.)

TABLE 8.7b

Optimum Spinal Irradiation Programme

Mean = 1200 counts	Bgd = 300 counts	C.V. _m = 1%
Now		
(I) 2 repeated measurements	C.V. _T = 2.38%	
or 2 x irradiation time	C.V. _T = 2.38%	
(II) 3 repeated measurements	C.V. _T = 1.95%	
or 3 x irradiation time	C.V. _T = 2.00%	

So little or nothing is gained by repeated irradiations in this case.

The three possible irradiation programmes are shown below:

	<u>C.V. τ of each measurement</u>	<u>Number of measurements</u>	<u>Time between measurements</u>	<u>Min. detectable change $p < 0.05$</u>
(a)	3.38	10	2 months	6.7%
(b)	2.38	6	4 months	5.7%
(c)	2.00	4	6 months	6.0%

it would be possible, with the stronger sources, simply to increase the irradiation time to improve the statistical error and hence reduce the time of each measurement considerably (Table 8.7b). From calculations of the standard error of percentage change, also in Table 8.7b, the best irradiation programme was thought to be a single measurement every four months over a 20 month period. The patient would then only be required for half an hour for each activation measurement.

No patient studies have been completed with the spine apparatus, though several are in progress. In addition to measuring calcium loss in the lumbar region, to evaluate different treatment regimes, comparisons are also being made with changes in forearm both with densitometry and neutron activation analysis. It is hoped fairly soon to include also a direct comparison with densitometry of the spine.

9

CONCLUSION.

CONCLUSION

The design of the apparatus for measurements of the peripheral bone was found to be successful for the sequential clinical studies that were performed on over one hundred patients. The purpose-built part body counter reduced the background radiation to levels that were acceptable when measuring ^{49}Ca . During the two and a half years that they were in regular use they were sufficiently stable and completely trouble free. In addition the patients did not complain of discomfort during forearm or tibia measurements.

The design of the forearm irradiation apparatus was improved upon after the initial set of measurements on renal patients although its use was continued for this group of patients. The use of a water bath, as combined premoderator and reflector into which the patient's arm was immersed, had several advantages over the first design. Firstly, the sensitivity of activation increased for a given dose. Secondly, the variations in induced activity due to overlying soft tissue from patient to patient were eliminated, increasing the possibility of absolute calcium measurement. Lastly, the precision of the measurement was improved when the water bath was used.

It was found that the activity of the original ^{252}Cf sources was sufficient for peripheral bone measurements when hydrogenous reflecting material was used in the irradiation apparatus. This value was much lower than the minimum activity necessary for patient measurements which

had been published by Boddy (1974b) and Evans (1976) who suggested 200 mCi and 500 mCi respectively. A total source strength of about 50 mCi therefore would be about the minimum activity required for peripheral calcium measurements if irradiation and detection apparatus similar to that described in this thesis were used.

The two methods used to analyse the patient spectra were compared quantitatively. It was found that the more complicated spectral stripping method, requiring a computer with at least 16K core to analyse the matrix algebra, was better than the simpler simultaneous equations method. This was so, both when the intrinsic accuracy was compared using a random variation of a single spectrum, and when the variation in a large number of sets of patient spectra were analysed. However the difference between the two techniques was not great, particularly when the water bath was used for irradiation. Thus although the matrix computer technique was superior and should be used where possible, it was not essential for ^{49}Ca measurements.

The irradiation programme that was adopted for the clinical studies produced good results but was rather time-consuming for both the operator and the patient. However the precision of each set of three measurements was very good, 1.5%, giving the least significant change that could be measured between two sets of measurements as 4.2% ($p < 0.05$). A single measurement with three times the source strength would give a precision of 2.2% but as the error due to movement was 1.9% an even stronger source would not approach the precision achieved by the existing

irradiation programme. The triple irradiations also provided a unique opportunity to obtain the precision of the techniques obtained from the actual measurements of the patients being studied.

The precision of calcium measurements of the forearm was better than that achieved by other methods of neutron activation analysis of peripheral bone. In addition the dose to the bone was in general less than that given by other techniques. A single measurement of calcium in the forearm using the water bath could be achieved with a precision of 2.51% and a maximum dose to the bone of 2 rem. Both the groups in Aberdeen and Orsay achieved poorer levels of precision for higher dose levels (Table 1.2), for their determination of calcium in the hand. Catto (1973a) stated a precision of 5% for a dose of 15 rem (Ettinger 1975) using an Am-Be source. Maziere (1976) achieved a precision of 3% for a dose of 8 rem using a combination of ^{252}Cf and Pu-Be. These dose levels were due mainly to the higher mean energy of the neutron spectra. The poorer levels of precision would probably be due to the inherent difficulties of measuring such a mobile organ as the hand. The group in Lyons (Guey et al 1976), the only other group to be using solely ^{252}Cf , gave a dose of 2 rem to the hand and obtained a similar number of calcium counts as were obtained by our forearm measurements. However, no figures for the precision of the method have been stated.

Comparison of the various techniques used for calcium

measurements of peripheral bone showed that the forearm was a better site for activation analysis than the hand, as far as the precision of measurement is concerned. It can also be seen that ^{252}Cf , with its relatively low mean neutron energy, was the ideal neutron source for the study of calcium in peripheral bones because of the lower dose given to the patient.

Although the characteristics of the apparatus for forearm measurements were very good and it was successfully used on a large number of patients, there are a number of ways in which it could be improved. The irradiation apparatus could be constructed in one section with the wax reflectors rigidly attached to the water bath. The perspex delivery tubes could enter the reflectors vertically, which would ensure that the sources would always be positioned at the ends of the delivery tubes. This would also enable the apparatus to be positioned adjacent to one wall and so be used with the spine apparatus in position.

In addition to peripheral sites, part body measurements of the spine were investigated. Extensive experiments showed that an adequate uniformity of measurement through the bodies of the lumbar vertebrae could be achieved using unilateral irradiation with ^{252}Cf and bilateral detection. Apparatus was constructed to irradiate patients using a modified dental chair with two ^{252}Cf sources either separated by 20 cm, or scanning a length of the spine. The tilting mechanism of the chair was used so that the weight of the patient held his back firmly and

comfortably in position; this apparatus was tested on a group of ten patients and it was found that calcium, but not phosphorus, could be satisfactorily measured.

The precision value of 2.4% for a skin dose of 6.6 rem and a bone dose of 0.7 rem compared very well with the two other published methods of spine calcium measurement; Al-Hiti (1976a) achieved a precision of 3% for a dose of 3 rem, whilst McNeill (1973b) obtained a figure of 6.4% for a dose of 0.4 rem. The latter technique, however, measured a large region 60 cm x 30 cm which included the pelvis and part of the ribs and sternum as well as the lower spine. A similar number of ^{49}Ca counts were obtained from the ^{252}Cf method and the cyclotron method (Al-Hiti et al 1976b), but although the cyclotron had a higher energy, the precision was worse because the patient sat upright for both activation and detection, a single crystal being used for the latter. The technique of McNeill (1973b) had a large figure for the reproducibility, probably due to the 30% less ^{49}Ca counts obtained and to the fact that a large, fixed length of the trunk was measured.

The characteristics of the ^{252}Cf method of lumbar spine measurement showed that bilateral detection and careful design of the irradiation apparatus could, to a large degree, compensate for the relatively low energy of neutrons from ^{252}Cf . A total source activity of 200 mCi was concluded to be sufficient for a 3 to 4 year clinical study of changes in the lumbar spine.

In addition to evaluating the technique of neutron activation analysis, the patient studies were designed to try and solve some important clinical problems. The following conclusions that are mentioned, illustrate the use of neutron activation analysis of the forearm as a research tool.

The vitamin D analogue, 1- α -hydroxycholecalciferol, was shown to increase significantly the bone calcium in patients undergoing haemodialysis. Such an increase was also found by Catto (1975), although he only performed measurements for 3 months on a smaller number of patients. This increase however, was found to stop after 8 months, and the net change over the next 8 months was approximately zero. Thus, 1- α -hydroxycholecalciferol is a suitable method of stabilising the bone calcium levels, although further studies may be necessary to determine whether the calcium level remains constant.

In a large group of patients on anticonvulsant therapy, no increase in calcium, denoting an improvement in their possible osteomalacia, was noted during treatment with either vitamin D₂ or D₃. This was contrary to the findings of Christiansen (1975) who used densitometric measurements of the forearm. In addition, absolute measurements of forearm showed that no calcium deficiency was present in the group as a whole, before vitamin D treatment was started, compared with normal controls. As our biochemical findings were in agreement with other workers, it would seem that there is evidence to suggest that anticonvulsant osteomalacia does not exist as such, but that the anticonvulsant

drugs may affect the biochemical parameters used to determine osteomalacia.

The results from the study on bipolar manic-depressive patients on lithium carbonate therapy suggested that there may be a calcium loss associated with this treatment. This study is a case where densitometry measurements would be expected to be different from neutron activation analysis. It was suspected that calcium may be lost, but it was known that the concentration of other elements increased; the latter was found to be so from densitometry measurements. The small number of patients make definite conclusions impossible.

The possibility of absolute calcium measurement was briefly investigated. Normalising the calcium counts, corrected for the ^{252}Cf activity, with the cube of the patient's height gave a variation of 12.1% (C.V.) for normal patients. This suggested that the normal range was too wide for use as a diagnostic tool for the individual patient, but that comparisons between groups would be possible. A significantly lower calcium level was measured in a group of patients with thyrotoxicosis, as would be expected, but not in the anticonvulsant group.

Neutron activation analysis was compared with other methods of monitoring bone mineral changes. Comparisons with densitometry of the forearm showed a reasonable correlation between changes measured by the two methods, $r = 0.41$ and $r = 0.38$, for the renal and epileptic groups. This was the first time that direct comparisons of the two

methods had been made at the same site and the figures were much better than the correlations between changes in forearm densitometry and whole body calcium of $r = 0.17$ and $r = 0.25$ found by Aloia (1975) and Cohn (1976) respectively. Such a comparison of the two techniques at the same peripheral site was valuable in ascertaining their relative merits. The degree of correlation however, was such that no definitive conclusion could be drawn. The level of correlation was neither high enough to say that the easier densitometric method is more suitable nor low enough to invalidate densitometry as a method for detecting calcium changes. Comparison of changes in metacarpal indices and neutron activation analysis showed no correlation between the two methods.

In conclusion, the value of part body neutron activation analysis by ^{252}Cf lies not in its use as a diagnostic tool, but as a research tool for specific clinical investigations of metabolic bone diseases.

APPENDICES.

APPENDIX I

Dosimetry Calculations

Ionization chambers give a measurement of the total neutron and gamma dose:

$$Fq = \frac{M}{WKS} \times D(t)$$

This equation comes from the Bragg-Gray relation where:

F = factor to correct for lack of saturation.

q = charge collected for tissue dose D(t).
t refers to tissue.

M = mass of gas in chamber.

W = energy per ion pair in the gas.

K = ratio of the kerma in tissue to the kerma
in the material of the chamber.

S = ratio of stopping powers of the wall to the
gas for secondary particles generated within
the walls of the chamber.

Now if ^{60}Co is used as a calibration source then M can be eliminated:

$$M = \frac{F_c q_c W_c K_c S_c}{D_c(t)}$$

where c refers to ^{60}Co

Now also $D(t) = D_\gamma(t) + D_n(t)$

and $q = q_\gamma + q_n$

$$\therefore D_n(t) = \frac{F_n W_n K_n S_n}{M} (q - q_y)$$

$$\therefore D_n(t) = \frac{q}{q_c} \frac{F_n}{F_c} \frac{W_n}{W_c} \frac{S_n}{S_c} \frac{K_n}{K_c} D_c(t) - \frac{F_n}{F_y} \frac{W_n}{W_y} \frac{K_n}{K_y} \frac{W_n}{W_y} D_y(t)$$

(N.P.L. 1974)

In this instance it is adequate to write this as:

$$D_n(t) = q \frac{F_n}{F_c} \frac{W_n}{W_c} \frac{S_n}{S_c} \frac{K_n}{K_c} \frac{D_c(t)}{q_c} - D_y(t) \dots (1)$$

Now $\frac{F_n}{F_c} = \frac{1.036}{1.022} = 1.014 \pm 1\%$ for the cylindrical chamber.

$\frac{F_n}{F_c} = \frac{1.016}{1.006} = 1.01 \pm 1\%$ for parallel plate chamber.

$\frac{W_n}{W_c} = 1.067 \pm 3\%$

$\frac{S_n}{S_c} = 0.988 \pm 1\%$

$\frac{D_c}{q_c} = 4.430 \pm 1\%$ for cylindrical chamber (over 2 years).

$\frac{D_c}{q_c} = 5.986 \pm 1\%$ for parallel plate chamber (over 3 years).

$K_c = 0.995$

(Lawson and Porter 1975)

The value q is measured experimentally leaving only the value K_n to be determined from the equation:

$$\overline{K}_n = \frac{\sum N(E) dE K^{\text{tissue}}(E)}{\sum N(E) dE K^{\text{chamber}}(E)} \dots (2)$$

The material of the chambers was 10.2% hydrogen and 89.8% carbon so the ratio $K^{\text{tissue}}/K^{\text{chamber}}$ could be calculated for any energy using the data of Bach and Caswell (1968). This was done at three different energies in the spectrum:

$$\text{At 2 MeV} \quad K_n = 0.9409$$

$$\text{At 0.38 MeV} \quad K_n = 0.9770 \quad (\text{This is approximately the mean energy of the spectrum})$$

$$\text{At 0.5 KeV} \quad K_n = 1.0005$$

Now there was little variation over the spectrum so a value $K_n = 0.977 \pm 3.5\%$ was chosen.

The error in the value of q was 1.04% from repeated measurements so the overall error in the $n + \gamma$ dose was approximately $\pm 6\%$.

APPENDIX II

Measurement of Thyroidal Iodine

Iodine can be measured by in-vivo activation analysis using the reaction $^{127}\text{I} (n, \gamma) ^{128}\text{I}$. The induced isotope ^{128}I decays with a half life of 25 min, and an energy 450 KeV. This low energy presents the main problem in the measurement of the iodine content of the thyroid because the background introduces a large error.

A total ^{252}Cf source strength of 45 mCi was used in the irradiation geometry shown in Figure A1. This had been found to be the optimum irradiation geometry for absolute iodine determination (Boddy et al 1974). The induced activity was measured using the part body counters with the thyroid collimators and a shadow shield behind the neckphantom (Fig. A1). Measurements were performed with two vials in the position of the lobes of the thyroid containing a combined total of 56 mg iodine. Dose measurements were performed using ionisation chambers and a geiger counter.

A 20 min irradiation, 100 s delay and 1000 s count produced the results below:-

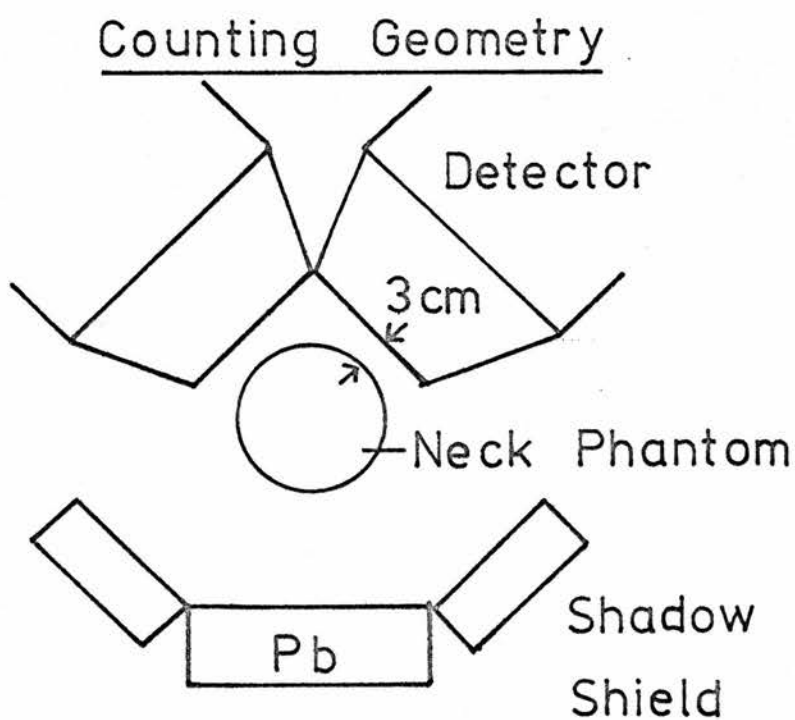
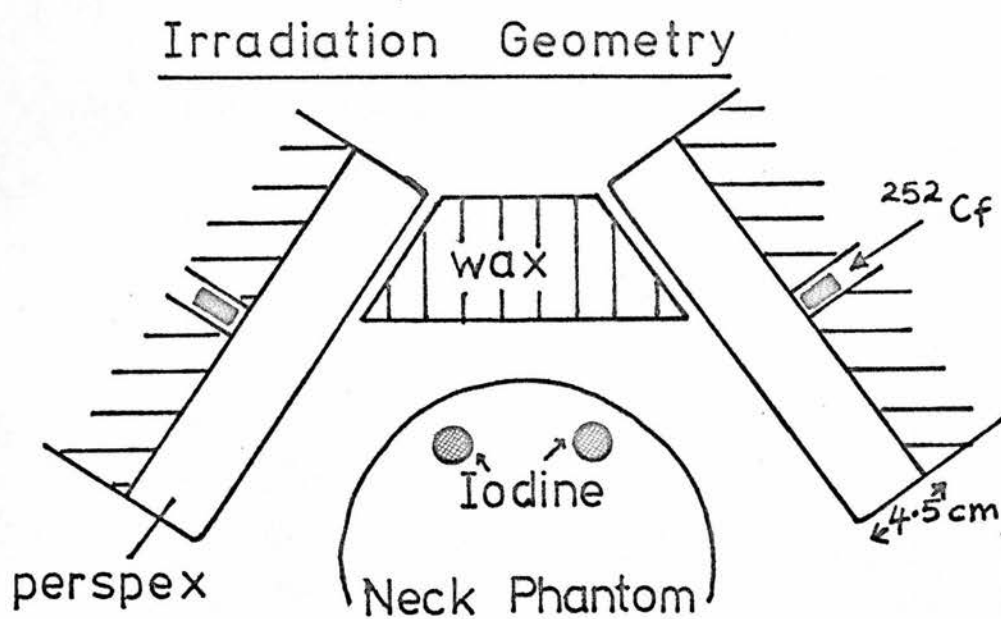
<u>Detected Counts:</u>	410 KeV-510 KeV
Background	5613
Background with Phantom	5832
Background plus Irradiated Phantom	9479
Net Iodine Counts	3647

Dose:

Skin Surface	8.3 rem
Thyroid	6.5 rem

Now the typical quantity of iodine in thyroid gland is 10 mg although if clinical studies were to be performed the quantity of iodine could be around 5 mg. The error, purely due to counting statistics, for a thyroid containing 10 mg I and 5 mg I would be 16.7% and 33.0% respectively. An increase in the irradiation time would increase the dose disproportionately to the increase in iodine activation due to the irradiation time being already similar to the half life of the induced iodine. This could be overcome by simply using ^{252}Cf sources of a higher activity.

Figure A1



APPENDIX III

Spectral Stripping Program

```
1 C# MAMATX 22/07/77          M MATRIX STRIPPING
2      PROGRAM MAMATX
3 C          SPECTRUM STRIPPING PROGRAM
4 C          PATIENT SPECTRUM IS SMOOTHED AND A MATRIX
5 C          TECHNIQUE IS USED TO SIMULTANEOUSLY FIT
6 C          THREE STANDARD SPECTRA TO THE WEIGHTED
7 C          PATIENT SPECTRUM USING A LEAST SQUARES METHOD.
8 C
9 C          AUTHOR : M.A.SMITH
10 C
11 C
12 C          SUBROUTINES CALLED,
13 C              MAPOLY
14 C              MAWEIT
15 C              MINV
16 C              MASHRL
17 C              MSHIFR
18 C              MSHIFL
19 C              MACHI2
20 C
21 C          -----!!-----
22 C
23 C          COMMON/ARRAYS/U(200),X(3),Y(200),Z(200),A(3,200)
24 C          COMMON/GRAF1/ITV(4096),XLOW,YLOW,XSCL,YSCL,X0,Y0,IDEV,FX,FY
25 C          COMMON/DATUM/CHI
26 C          DIMENSION AU(3,200),AUATAW(3,200),AWAT(3,3),LL(3),MM(3),PAT(20)
27 C          DATA ITEST/1HY/,PAT/20*1H /
28 C          VV=1.
29 C          V=1.
30 C          NCALC=0
31 C
32 C          INITIALISE ARRAYS
33 C
34 C          DO 300 I=1,3
35 C              X(I)=0.
36 C              LL(I)=0
37 C              MM(I)=0
38 C              DO 290 J=1,3
39 C                  AWAT(I,J)=0.
40 C          290 CONTINUE
41 C              DO 300 K=1,200
42 C                  A(I,K)=0.
43 C                  AU(I,K)=0.
44 C                  AUATAW(I,K)=0.
45 C          300 CONTINUE
46 C              DO 310 I=1,200
47 C                  Z(I)=0.
48 C                  Y(I)=0.
49 C                  W(I)=0.
50 C          310 CONTINUE
51 C
52 C          INPUT DATA
53 C
54 C          WRITE(1,100)
55 C          100 FORMAT(' SPECTRAL STRIPPING')
56 C          WRITE(1,108)
57 C          108 FORMAT(' CALCIUM 360/406 ')
58 C          READ(1,107)CAL
59 C          107 FORMAT(F8.0)
60 C          DO 1 I=1,3
61 C              WRITE(1,98)
62 C          98 FORMAT(' INPUT CL,NL,CA ')
63 C          READ(3,99) DUM
64 C          99 FORMAT(A1)
65 C          READ(3,101)W
66 C          101 FORMAT(SX,8F7.0)
67 C          DO 2 J=1,200
68 C              2 A(I,J)=W(J)
69 C          READ(1,113) NAME
70 C          1 CONTINUE
```

```

71 C
72 C
73 C
74 C      10 READ(3,89) PAT
75 C      89 FORMAT(20A4)
76 C      WRITE(9,88)PAT
77 C      88 FORMAT('0 ',20A4)
78 C      READ(3,101)Y
79 C      DO 50 I=1,200
80 C      50 IF(Y(I).GE.900000.)Y(I)=0.
81 C
82 C      SMOOTH THE COMPLEX SPECTRUM
83 C      CALL MAPOLY
84 C      WRITE(1,106)Y
85 C
86 C      SET UP WEIGHTS FOR THIS RUN
87 C
88 C      CALL MAWEIT
89 C
90 C      GENERATE A.W
91 C
92 C      14 DO 3 I=1,3
93 C      DO 3 J=1,200
94 C      3 AW(I,J)=A(I,J)*W(J)
95 C
96 C      GENERATE A.W,A(TRANPOSE)
97 C
98 C      DO 5 I=1,3
99 C      DO 5 J=1,3
100 C      AWAT(I,J)=0.
101 C      DO 6 K=1,200
102 C      AWAT(I,J)=AWAT(I,J)+AW(I,K)*A(J,K)
103 C      6 CONTINUE
104 C      5 CONTINUE
105 C
106 C      INVERT
107 C
108 C      CALL MINV(AWAT,3,D,LL,MM)
109 C      IF(D.NE.0.)GO TO 11
110 C      WRITE(1,105)
111 C      105 FORMAT(' SINGULAR MATRIX !')
112 C      NCALC=NCALC+1
113 C      GO TO 10
114 C
115 C      MULTIPLY (AWAT)**-1 BY A.W AND Y
116 C      TO GIVE X
117 C
118 C      11 DO 7 I=1,3
119 C      DO 7 J=1,200
120 C      AWATAW(I,J)=0.
121 C      DO 8 K=1,3
122 C      AWATAW(I,J)=AWATAW(I,J)+AWAT(I,K)*AW(K,J)
123 C      8 CONTINUE
124 C      7 CONTINUE
125 C      DO 9 I=1,3
126 C      X(I)=0.
127 C      DO 9 J=1,200
128 C      9 X(I)=X(I)+AWATAW(I,J)*Y(J)
129 C      NCALC=NCALC+1
130 C      WRITE(1,102)NCALC
131 C      102 FORMAT(' RESULTS OF DATA NO',I2)
132 C      WRITE(1,103)X
133 C      103 FORMAT(' X VECTOR :',3E20.6)
134 C      IF(VV.EQ.1.) GO TO 104
135 C      WRITE(9,102)NCALC
136 C      WRITE(9,103)X
137 C      109 FORMAT(' CHI-SQUARED ',E13.6)
138 C      104 CONTINUE
139 C
140 C      SHIFT STANDARDS

```

```

141 C
142 IF(VV.EQ.2.) GO TO 15
143 C BY HAND---
144 C CALL MASHIF(VV)
145 C OR AUTOMATICALLY
146 C CALL MASHRL(VV)
147 NCALC=NCALC-1
148 GO TO 14
149 15 CONTINUE
150 C
151 C DISPLAY COMPLEX-STANDARDS
152 C
153 C CALL MAOUT
154 C
155 V=1.
156 V=2.
157 C WRITE(1,106)Y
158 106 FORMAT(6(2X,F8.4))
159 C
160 C CALC. CHI-SQUARED
161 C
162 CALL MACHI2
163 WRITE(9,109) CHI
164 CAL2=CALXX(3)
165 WRITE(9,107) CAL2
166 C
167 V=1.
168 VV=1.
169 WRITE(1,112)
170 112 FORMAT(' ANOTHER SPECTRUM?')
171 READ(1,113) NAME
172 113 FORMAT(A1)
173 IF(NAME.EQ.ITEST) GO TO 10
174 CONTINUE
175 END

```

```

1 C# MAPOLY 22/07/77      M POLYNOMIAL SMOOTHING
2   SUBROUTINE MAPOLY
3   COMMON/ARRAYS/W(200),X(3),Y(200),Z(200),A(3,200)
4   DIMENSION IY(200)
5   DO 130 I=1,200
6   W(I)=0.
7   IY(I)=0
8   IY(I)=INT(Y(I)/4.0)
9   130 CONTINUE
10  WRITE(1,10)
11  10 FORMAT(' NO. OF POINTS FOR SMOOTHING')
12  NO=13
13  C READ(1,20) NO
14  20 FORMAT(I2)
15  IF(NO.EQ.15) GO TO 60
16  IF(NO.EQ.13) GO TO 50
17  IF(NO.EQ.11) GO TO 40
18  IF(NO.EQ.00) GO TO 1000
19  30 K0=59
20  K1=54
21  K2=39
22  K3=14
23  K4=-21
24  K5=0
25  K6=0
26  K7=0
27  KM=231
28  GO TO 100
29  40 K0=39
30  K1=34
31  K2=69
32  K3=44
33  K4=9
34  K5=-36
35  K6=0
36  K7=0
37  KM=429
38  GO TO 100
39  50 K0=25
40  K1=24
41  K2=21
42  K3=16
43  K4=9
44  K5=0
45  K6=-11
46  K7=0
47  KM=143
48  GO TO 100
49  60 K0=167
50  K1=162
51  K2=147
52  K3=122
53  K4=87
54  K5=42
55  K6=-13
56  K7=-78
57  KM=1105
58  100 DO 110 I=8,193
59  IA=K7*IY(I-7)+K6*IY(I-6)+K5*IY(I-5)
60  IB=K4*IY(I-4)+K3*IY(I-3)+K2*IY(I-2)
61  IC=K1*IY(I-1)+K0*IY(I)+K1*IY(I+1)
62  ID=K2*IY(I+2)+K3*IY(I+3)+K4*IY(I+4)
63  IE=K5*IY(I+5)+K6*IY(I+6)+K7*IY(I+7)
64  XDUM=(FLOAT(IA+IB+IC+ID+IE))/(FLOAT(KM))
65  W(I)=XDUM*4.0
66  110 CONTINUE
67  DO 120 I=1,200
68  Y(I)=W(I)
69  120 CONTINUE
70  DO 140 I=1,200
71  W(I)=0.
72  140 CONTINUE
73  1000 RETURN
74  END

```

```

1 C# MAWEIT 22/07/77          M WEIGHTING FACTORS, STANDARDS AND PATIENT
2      SUBROUTINE MAWEIT
3      COMMON/ARRAYS/U(200),X(3),Y(200),Z(200),A(3,200)
4      C
5      C          OVERALL WEIGHTING FACTOR
6      C
7      C      WRITE(1,100)
8      100  FORMAT(' WEIGHTING CODE:1:1,2:1/Y,3:1/SQRT(Y)  WEIGHT:1:1')
9      C      READ(1,110) N
10     110  FORMAT(I1)
11     C
12     N=3
13     C
14     DO 1 I=1,200
15     IF(Y(I).LE.0.) Y(I)=0.
16     IF(N=2)10,20,30
17     10  W(I)=1.
18     GO TO 1
19     20  CONTINUE
20     IF(Y(I).NE.0.) GO TO 25
21     Y(I)=1.
22     25  W(I)=1./Y(I)
23     GO TO 1
24     30  W(I)=SQRT(Y(I))
25     1  CONTINUE
26     C
27     C          INDIVIDUAL WEIGHTING FOR EACH PEAK
28     C
29     C      WRITE(1,120)
30     120  FORMAT(' CL:NA:CA RATIO:1:')
31     C      READ(1,130)K,L,M
32     130  FORMAT(3I2)
33     C
34     K=1
35     L=5
36     M=9
37     C
38     DO 40 I=1,89
39     40  W(I)=W(I)*FLOAT(K)
40     DO 50 I=90,139
41     50  W(I)=W(I)*FLOAT(L)
42     DO 60 I=140,200
43     60  W(I)=W(I)*FLOAT(M)
44     RETURN
45     END

```

```

1 C# MINV 25/07/77 M MATRIX INVERSION
2 SUBROUTINE MINV(A,N,D,L,M)
3 DIMENSION A(N),L(N),M(N)
4 C
5 C GAUSS-JORDAN METHOD OF MATRIX
6 C INVERSION. DETERMINANT IS
7 C RETURNED IN ARGUMENT D AND
8 C IF D IS ZERO ON EXIT IT INDICATES
9 C THAT A WAS SINGULAR.
10 C
11 C SEARCH FOR LARGEST ELEMENT
12 C
13 D=1.
14 NK=-N
15 DO 80 K=1,N
16 NK=NK+N
17 L(K)=K
18 M(K)=K
19 KK=NK+K
20 BIGA=A(KK)
21 DO 20 J=K,N
22 IZ=N*(J-1)
23 DO 20 I=K,N
24 IJ=IZ+I
25 10 IF(ABS(BIGA)-ABS(A(IJ)))15,20,20
26 15 BIGA=A(IJ)
27 L(K)=I
28 M(K)=J
29 20 CONTINUE
30 C
31 C INTERCHANGE ROWS
32 C
33 J=L(K)
34 IF(J-K)35,35,25
35 25 KI=K-N
36 DO 30 I=1,N
37 KI=KI+N
38 HOLD=-A(KI)
39 JI=KI-K+J
40 A(KI)=A(JI)
41 30 A(JI)=HOLD
42 C
43 C INTERCHANGE COLUMNS
44 C
45 I=M(K)
46 IF(I-K)45,45,38
47 38 JP=N*(I-1)
48 DO 40 J=1,N
49 JK=NK+J
50 JI=JP+J
51 HOLD=-A(JK)
52 A(JK)=A(JI)
53 40 A(JI)=HOLD
54 C
55 C DIV COL BY -PIVOT (VAL OF PIVOT
56 C IS IN BIGA
57 C
58 45 IF(BIGA)48,46,48
59 46 D=0.
60 RETURN
61 48 DO 55 I=1,N
62 IF(I-K)50,55,50
63 50 IK=NK+I
64 A(IK)=A(IK)/(-BIGA)
65 55 CONTINUE
66 C
67 C REDUCE MATRIX
68 C
69 DO 65 I=1,N
70 IK=NK+I
71 HOLD=A(IK)
72 IJ=I-N
73 DO 65 J=1,N
74 IJ=IJ+N

```



```

75      IF(I-K)60,65,60
76      60 IF(J-K)62,65,62
77      62 KJ=IJ-I+K
78      A(IJ)=HOLD*A(KJ)+A(IJ)
79      65 CONTINUE
80 C
81 C      DIV ROW BY PIVOT
82 C
83      KJ=K-N
84      DO 75 J=1,N
85      KJ=KJ+N
86      IF(J-K)70,75,70
87      70 A(KJ)=A(KJ)/BIGA
88      75 CONTINUE
89 C
90 C      PRODUCT OF PIVOTS
91 C
92      D=D*BIGA
93 C
94 C      REPLACE PIVOT BY RECIPROCAL
95 C
96      A(KK)=1./BIGA
97      80 CONTINUE
98 C
99 C      FINAL ROW AND COL INTERCHANGE
100 C
101      K=N
102      100 K=(K-1)
103      IF(K)150,150,105
104      105 I=L(K)
105      IF(I-K)120,120,108
106      108 JQ=N*(K-1)
107      JR=N*(I-1)
108      DO 110 J=1,N
109      JK=JQ+J
110      HOLD=A(JK)
111      JI=JR+J
112      A(JK)=-A(JI)
113      110 A(JI)=HOLD
114      120 J=M(K)
115      IF(J-K)100,100,125
116      125 KI=K-N
117      DO 130 I=1,N
118      KI=KI+N
119      HOLD=A(KI)
120      JI=KI-K+J
121      A(KI)=-A(JI)
122      130 A(JI)=HOLD
123      GO TO 100
124      150 RETURN
125      END

```

```

1 C+ MASHRL 22/07/77      M AUTO STD SHIFT
2      SUBROUTINE MASHRL(VV)
3      COMMON/ARRAYS/W(200),X(3),Y(200),Z(200),A(3,200)
4      COMMON/DATUM/CHI
5 C
6 C      SHIFT STANDARDS
7 C
8      IF(VV.EQ.2.) GO TO 260
9      DO 240 J=1,3
10     JJ=J
11     CALL MACH12
12     WRITE(1,108)
13     108 FORMAT(' SHIFT STD. ')
14 C
15     DUM=CHI
16     CALL MSHIFL(JJ)
17     CALL MACH12
18     IF(CHI.LT.DUM) GO TO 210
19     GO TO 220
20 C
21 C
22     210 DUM=CHI
23     CALL MSHIFL(JJ)
24     CALL MACH12
25     IF(CHI.LT.DUM) GO TO 210
26     CALL MSHIFR(JJ)
27     CALL MACH12
28     GO TO 240
29 C
30 C
31     220 DUM=CHI
32     CALL MSHIFR(JJ)
33     CALL MACH12
34     IF(CHI.LT.DUM) GO TO 220
35     CALL MSHIFL(JJ)
36     CALL MACH12
37 C
38     240 CONTINUE
39     WRITE(1,110)
40     110 FORMAT(' STDS CORRECTED ')
41     VV=2.
42     260 CONTINUE
43     RETURN
44     END

```

```

1 C# MSHIFR 22/07/77          M INCREMENT RIGHT TO CORRECT FOR DRIFT
2   SUBROUTINE MSHIFR(JJ)
3   COMMON/ARRAYS/W(200),X(3),Y(200),Z(200),A(3,200)
4   COMMON/DATUM/CHI
5   C
6   C      SHIFT STD TO RIGHT
7   C
8   DO 10 I=1,199
9   L=201-I
10  H=200-I
11  J=JJ
12  A(J,L)=A(J,M)
13  10 CONTINUE
14  C
15  WRITE(1,110)
16  110 FORMAT(' RIGHT ')
17  RETURN
18  END

```

```

1 C# MSHIFL 22/07/77          M INCREMENT LEFT TO CORRECT FOR DRIFT
2   SUBROUTINE MSHIFL(JJ)
3   COMMON/ARRAYS/W(200),X(3),Y(200),Z(200),A(3,200)
4   COMMON/DATUM/CHI
5   C
6   C      SHIFT STD TO LEFT
7   C
8   DO 10 I=1,199
9   J=JJ
10  A(J,I)=A(J,I+1)
11  10 CONTINUE
12  C
13  WRITE(1,110)
14  110 FORMAT(' LEFT ')
15  RETURN
16  END

```

```

1 C# MACH12 22/07/77          M CHI-SQUARED CALCULATION
2   SUBROUTINE MACH12
3   COMMON/ARRAYS/W(200),X(3),Y(200),Z(200),A(3,200)
4   COMMON/DATUM/CHI
5   C
6   C      CALCULATE CHI-SQUARED
7   C
8   DO 11 J=1,200
9   Z(J)=0.
10  Z(J)=Y(J)
11  11 CONTINUE
12  DO 12 I=1,3
13  DO 12 J=1,200
14  Z(J)=Z(J)-(X(I)*A(I,J))
15  12 CONTINUE
16  CHI=0.
17  DO 13 I=20,190
18  C=0.
19  DO 22 J=1,3
20  C=C+(X(J)*A(J,I))
21  22 CONTINUE
22  CHI=CHI+(Z(I)*Z(I))/C
23  13 CONTINUE
24  WRITE(1,111) CHI
25  111 FORMAT(' CHI-SQUARE: ',E13.6)
26  CONTINUE
27  RETURN
28  END

```

APPENDIX IV

Measurement of Phosphorus in the Spine

Phosphorus is measured by detecting the induced ^{28}Al which is produced via an n, γ reaction which has a threshold at 2.3 MeV. Calculations were made of the neutron spectrum (Section 2.6) of ^{252}Cf at different depths of premoderation and the following results obtained:

Thickness of premoderation	% of neutrons at that depth with energy > 2.3 MeV (approximately)
0	47%
3	19.5%
5	12%
7	6.7%

Out of the 10 patients measured, a reasonably large phosphorus peak was seen in 5 cases. These five patients were either of small stature with little overlying soft tissue or they had an artificial hip. This suggests that the peak was due to the activation of phosphorus in the spinous processes at a depth where there would be sufficient neutrons with energy > 2.3 MeV. Alternatively, it could be due in part to a contribution from the reaction $^{27}\text{Al}(n, \gamma)^{28}\text{Al}$ from aluminium in the artificial joint.

Thus phosphorus measurements at a depth of 5 cm - 9 cm, the position of the body of the vertebrae, are not possible using ^{252}Cf .

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